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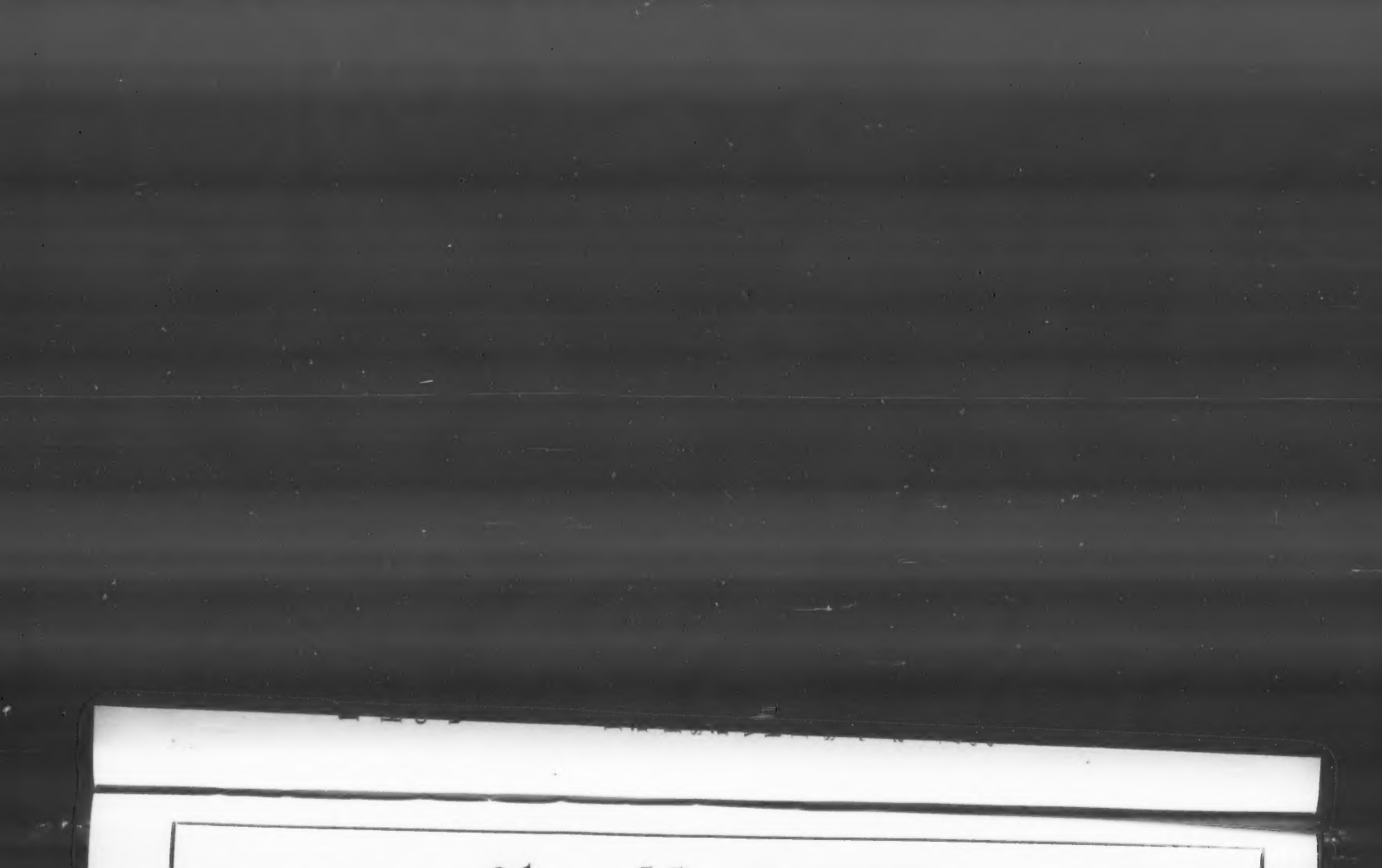

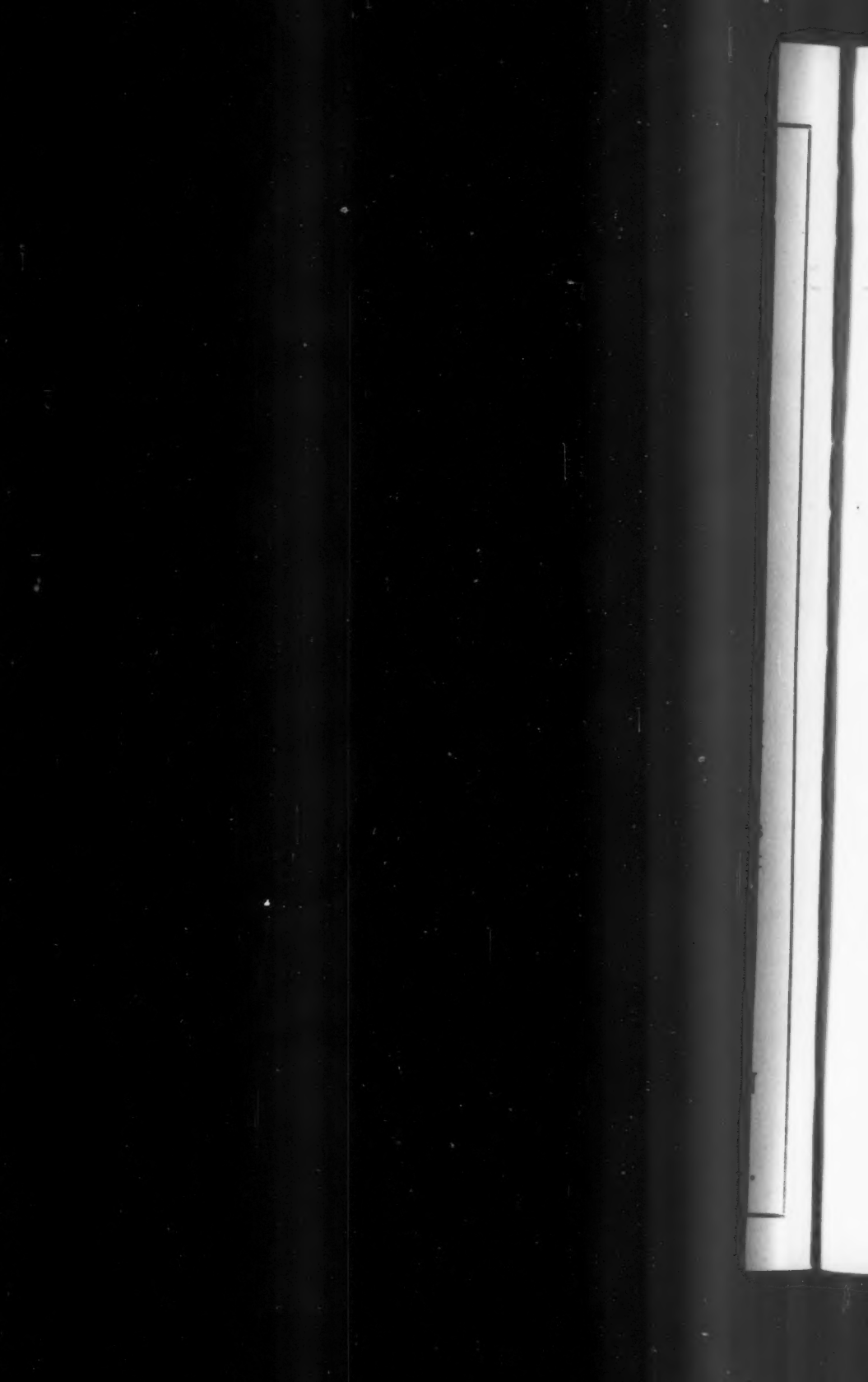

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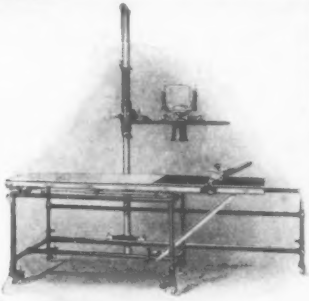

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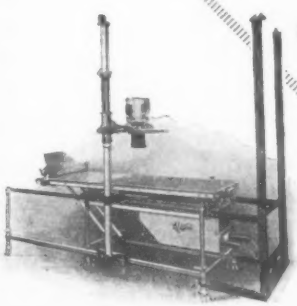

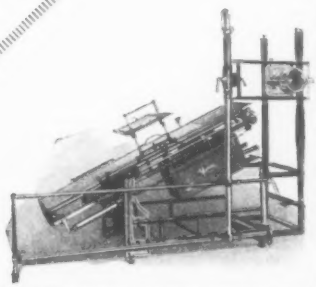

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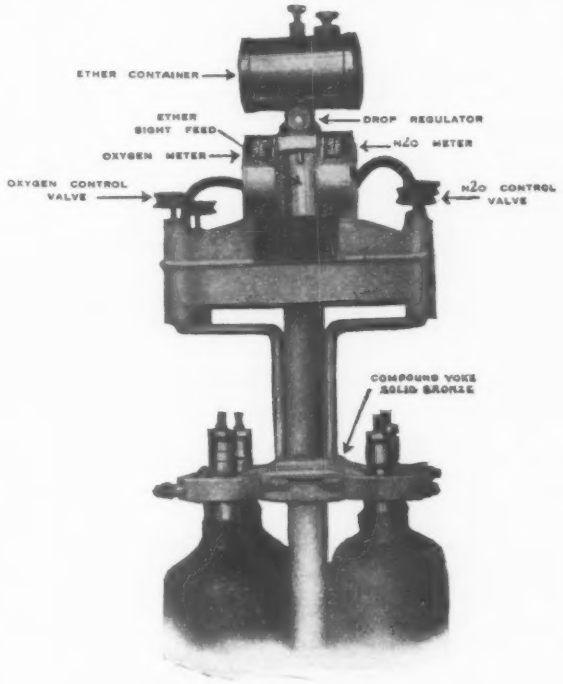

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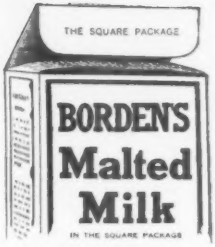

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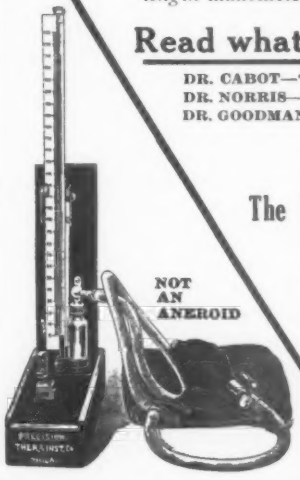

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ORIGINAL ARTICLES

THE COMPARATIVE VALUE OF THE WASSERMANN, THE COLLOIDAL GOLD AND OTHER SPINAL FLUID TESTS: A STUDY OF 203 CASES.[1]

By E. M. Hammes, M.D.,

ASSISTANT PROFESSOR IN NERVOUS AND MENTAL DISEASES, UNIVERSITY OF MINNESOTA, ST. PAUL, MINN.

Both clinical studies and laboratory investigations, especially in the past few years, have increased our diagnostic ability in organic nervous diseases to a marked degree. New methods and tests have been added in rapid succession. Since the introduction of the lumbar puncture by Quincke, in 1891, the examination of the spinal fluid has become more and more frequent, and at the present time no neurologist has scientifically completed his study of a doubtful neurological case unless he has made a thorough and comprehensive study of the spinal fluid.

The routine study of the spinal fluid comprises a cell count, a globulin test, a Fehling test, a Wassermann, a colloidal gold test and an examination for bacteria when indicated. In our work Dr. Riggs, Dr. Michael and myself have followed this routine examination as closely as possible in order to estimate the comparative value of the various tests in syphilitic and non-syphilitic diseases of the central nervous system. The cell count was made in the Fuchs-Rosenthal counting chamber and a diluting fluid containing methyl violet was used.

[1] Thesis, read before the Minnesota Academy of Medicine, October 11, 1916.

In testing for increased globulin we used:

(*a*) *The Nonne Test.* By adding equal parts of spinal fluid with a neutral hot saturated solution of ammonium sulphate. Cloudiness within three minutes means a positive test.

(*b*) *Noguchi Test.* Take one part spinal fluid, add 4 parts 10 per cent. butyric acid, let come to a boil, add one part normal NaOH, let come to a boil. A positive test gives a flocculent precipitate within one-half hour.

(*c*) *Pandy's Test.* Take from 0.5 to 1 c.c. of a saturated aqueous solution of carbolic acid and add to it one drop of spinal fluid. The immediate formation of a bluish-white ring or cloud means an increased amount of globulin in the spinal fluid. For the most part these three reactions have been parallel. I personally prefer the Noguchi test, probably because I have used it more frequently than the others.

The Fehling Test. The Fehling test did not reveal anything of diagnostic value. It was positive in practically all cases.

The Colloidal Gold Test. This test was first introduced by Lange in 1912. Its principle depends upon the protective action of certain colloids, especially proteins, on the precipitation of gold suspensions by sodium chloride. Lange found that a 0.4 per cent. pure sodium chloride solution was of sufficient strength to keep the normal spinal fluid proteins in solution, but too weak to cause flocculation of colloidal gold solutions. In abnormal spinal fluids, on account of their high protein content, one naturally expected a greater degree of protection. However, this was not the case, and Lange observed that partial or complete precipitation of colloidal gold with resultant color changes was produced by these fluids with almost definite curves, especially from those spinal fluids of luetic origin. Fluids from tabes and cerebrospinal lues gave their maximal reactions in the lower dilutions, and this change has been so constant that it is spoken of as the "luetic zone" and "luetic curve;" fluids from the different types of meningitis gave reactions with their greatest intensity in the higher dilutions, commonly known as "Verschiebung nach oben;" fluids from paretics caused complete flocculation in the first four to six tubes with such regularity that Miller and Levy suggested the term "paretic curve." In Lange's original conclusions he states that normal cerebrospinal fluid produces no color changes in any dilution in the colloidal gold solution. Most workers, however, believe that slight color changes up to a purple color can occur in an absolutely normal spinal fluid. The colloidal gold test is very simple to perform, is readily interpreted, and requires only 0.2 c.c. cerebrospinal fluid. However, the preparation of the colloidal gold solution is most difficult. Frequently an apparently excellent solution is worthless. Miller and his co-workers have adopted the following standards:

2536 C 1 23 My 44

1. The solution must be absolutely transparent and preferably of a brilliant red-orange or salmon-red color.

2. Five c.c. of the solution must be completely precipitated by 1.7 c.c. of a 1 per cent. sodium chloride solution in the time interval of one hour.

3. The solution must be neutral in reaction on the day on which it is used.

4. It must give a typical reaction curve with a known paretic cerebrospinal fluid.

5. It must produce no reaction greater than a No. 1, with a known cerebrospinal fluid.

It frequently requires four or five attempts before a satisfactory solution is procured. The colloidal gold solution may be prepared in three different ways:

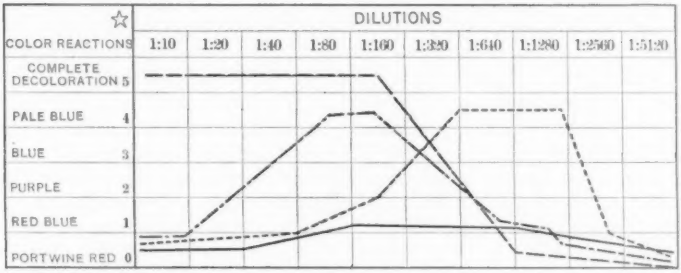
Lange's Method. Take 1000 c.c. of fresh doubly distilled water, add 10 c.c. of a 1 per cent. Merck's gold chloride solution and 10 c.c. of a 2 per cent. solution of K_2CO_3. Heat rapidly to the boiling-point, stir vigorously, and add 10 c.c. of a 1 per cent. solution of formalin. The colorless solution must at once assume a clear port-wine color.

Eike's Method. Take 1000 c.c. of fresh doubly distilled water, add 10 c.c. of a 1 per cent. solution of Merck's gold chloride and 5 c.c. of a 5 per cent. dextrose solution. Heat to 90° to 95° and then add a 5 per cent. solution of K_2CO_3, one drop at a time, until the required color is secured.

Oetiker's Modification of Eike's Method. Oetiker believed that the failures in procuring proper solution were due to two factors: (1) the variation in temperature, and (2) the variable amount of alkali solution added. He uses Eike's method; heats the solution to exactly 90° and without turning off the flame adds at once 12 c.c. of a 2 per cent. K_2CO_3 solution. With this method he has had no difficulty in getting satisfactory solutions. We have used most frequently Lange's method and of late Oetiker's modification of Eike's method; the latter is very satisfactory. The test is made as follows: Take eleven small test-tubes, carefully cleaned. In the first one put 1.8 c.c. of a fresh sterile 0.4 per cent. NaCL solution. In the remaining ten tubes put 1 c.c. of the same sodium chloride solution. To the first tube add 0.2 c.c. of the spinal fluid to be tested, making a dilution of 1 to 10. Mix thoroughly and transfer 1 c.c. from tube 1 to tube 2, again mix thoroughly and transfer 1 c.c. from tube 2 to tube 3, continue this process up to and including the tenth tube. This gives a series of dilutions ranging from 1 to 10 in tube 1 to 1 to 5120 in tube 10. Now add to each of the eleven tubes 5 c.c. of a satisfactory colloidal gold solution. Shake thoroughly and make readings in one-half hour and again in twenty-four hours. There is rarely any difference except of intensity between the half-hour and twenty-four-hour reading. The readings

are tabulated in numericals from 0 to 5 : 0 meaning no color change; 1 a red blue; 2 a purple; 3 a blue; 4 a pale blue; 5 a complete decolorization.

The four typical curves are demonstrated in the following table:



—— No or slight change. Normal spinal fluid.
. . . . Meningitic curve or "Verschiebung nach oben."
-.-.- Leutic curve.
– – – Paretic curve.
Chart taken from article reference No. 16.

According to Lange the presence of blood in the spinal fluid causes color changes in the first four tubes. This is very important, for occasionally one procures a bloody spinal fluid, due to the lumbar puncture. We have repeatedly tested spinal fluids containing blood, either accidentally or added directly, in order to determine this point. Very small amounts of blood caused absolutely no change in the colloidal gold curve different from that produced by spinal fluid alone. However, when enough blood was present to make the spinal fluid distinctly hemorrhagic there was a marked color change in the first four to six tubes. This is in accord with Oetiker's observations. If a spinal fluid is kept sterile, age has no effect on the colloidal gold test. Oetiker examined a paretic spinal fluid which he had kept on ice for over one year. The same typical paretic curve was produced as at the first examination. However, Flesh has observed that in spinal fluids over eight days old the intensity of the colloidal gold curve is greater.

The Wassermann Test. In doing our Wassermann test we use for antigen an alcoholic extract of human heart. In our experience the cholesterinized antigen is so sensitive that we have obtained positive findings in apparently normal cases when other antigens also gave negative findings. Of course, there is the possibility of getting a negative test in weakly positive cases with an antigen similar to the one we use. We inactivate all sera, but use the spinal fluids direct in quantities from 0.02 to 1 c.c. In a few negative cases we have used larger amounts with rather unsatisfactory results.

This paper comprises the study of 203 cases: 43 paresis, 34 tabes, 27 cerebrospinal lues, 4 congenital lues, 11 meningitis, 3 tetanus,

and 81 other non-luetic organic and functional conditions. In the luetic cases the report of the first examination is given before active antisyphilitic treatment was commenced. All the tests have been most intense and constant in general paresis.

GENERAL PARESIS—43 CASES.

Case No.	Wasserman.		Colloidal gold test.	Globulin.		Lympho-cytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
15	+	+	5543200000	+	+	64	
19	+	+	4555420000	+	+	92	
29	+	+	5554400000	+	+	24	
30	+	+	5555544432	+	+	106	
31	+	+	5543200000	+	+	42	
32	+	+	5554420000	+	+	12	
33	+	+	5455400000	+	+	16	
34	+	+	5554321000	+	+	29	
35	+	+	5555430000	+	+	83	
36	+	+	5555555555	+	+	37	Acutely maniacal type.
37	+	+	5554200000	+	+	44	
38	+	+	5555421000	+	+	9	
39	+	+	4554200000	+	+	32	
40	+	+	5555430000	+	+	12	
41	+	+	5554210000	+	+	17	
42	+	+	5532000000	+	+	115	
58	+	+	5544311000	+	+	62	
64	+	+	5555410000	+	+	6	
65	+	+	5544300000	+	+	34	
67	0	+	5554320000	+	+	23	
68	+	+	5554310000	+	+	29	
69	+	+	5544420000	+	+	81	
70	+	+	4554430000	+	+	37	
81	+	+	5555430000	+	+	63	
82	0	0	0122200000	Mild	Mild	14	Typical clinical paresis
112	+	+	5555554200	+	+	4	
122	+	+	5555432000	+	+	28	
126	+	+	4555420000	+	+	16	Frequent epilepsy.
136	+	+	5554320000	+	+	46	
139	+	+	5555543100	+	+	38	
150	+	+	5543300000	+	+	6	
154	+	+	5555420000	+	+	8	
161	0	0	5544410000	+	+	64	Grandiose type.
165	+	+	5554300000	+	+	14	
169	0	+	5544421000	+	+	28	
182	+	+	5543100000	+	+	16	
183	+	+	4555430000	+	+	22	
184	+	+	5555555555	+	+	78	Grandiose type.
191	+	+	5543100000	+	+	6	
196	+	+	5554310000	+	+	18	
198	+	+	5544320000	+	+	20	
201	+	+	5554321000	+	+	68	
202	+	+	4554300000	+	+	74	

The characteristic paretic curve of the colloidal gold reaction was found in 42 cases out of 43 spinal fluids examined. Case 82, a typical clinical case of paresis, gave normal blood and spinal fluid findings, and under antiluetic treatment intraspinally made an apparent clinical recovery up to the present time (ten months ago). He had contracted syphilis twenty-two years previous. It is quite possible that we were dealing with a case of cerebrospinal

lues. Subsequent tests made after vigorous treatment showed no change from the first one. One case (No. 161) gave a typical paretic curve with a negative blood and spinal fluid. This case is one of the grandiose type and is clinically undoubted paresis. Case 36 (acutely maniacal type) and Case 184 (grandiose type) were interesting in that they gave complete decolorization in all dilutions. Four of our cases gave a negative Wassermann in the blood; all showed a marked positive globulin test; all but 5 had a lymphocytosis of over ten cells per cubic millimeter. In a study of 130 cases of paretic spinal fluids, Miller and his co-workers found a typical paretic colloidal gold curve 127 times. Of the three atypical reactions, 1 occurred in a very early case, 1 was probably due to an old and infected spinal fluid, and 1 was made after vigorous intraspinal therapy. Other workers do not place as much diagnostic value on this curve. Swalm and Mann and Solomon and Welles, although they found it present in a large majority of their paretics, question its true specificity.

TABES—34 CASES.

Case No.	Wassermann.		Colloidal gold test.	Globulin.		Lympho-cytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
6	0	+	3343210000	+	+	16	
9	+	+	5554210000	+	+	38	No signs of paresis.
10	+	+	3334200000	+	+	8	
4	0	0	3443210000	+	+	3	Typical clinical case.
12	+	+	1233210000	+	+	16	
13	+	+	2334310000	+	+	6	
18	+	+	3443210000	+	+	23	
54	0	0	1232100000	0	0	3	Typical case with positive history.
56	+	+	4432100000	+	+	18	
57	+	+	3244210000	+	+	69	
59	+	+	2342123432	+	+	38	
60	+	+	3444310000	+	+	26	
62	+	+	4432100000	+	+	9	
63	+	+	5554321000	+	+	18	Suspected taboparesis
83	0	0	0122210000	0	0	3	Typical clinical case.
86	+	+	2343200000	+	+	79	
87	+	+	4433210000	+	+	16	
88	+	+	3444321000	+	+	8	
109	+	+	2344431000	+	+	19	
124	+	+	1234300000	+	+	6	
125	+	+	4433210000	+	+	32	
155	+	+	5342100000	+	+	8	
170	+	+	2344310000	+	+	26	Gastric crises only.
173	+	+	4432200000	+	+	18	
179	+	+	3344210000	+	+	36	
181	+	+	3334110000	+	+	28	
185	+	+	3444200000	+	+	6	
186	0	+	4322210000	+	+	18	
187	0	0	3444320000	+	+	9	
188	0	+	2223210000	+	+	3	
193	+	+	3443320000	+	+	12	
195	+	+	4342100000	+	+	36	
200	+	+	3443100000	+	+	94	

In our series of 34 cases of tabes we found a positive globulin test in all cases but 2, a lymphocytosis above ten twenty-two times, a positive Wassermann in the spinal fluids in all cases but 4, and a positive Wassermann in the blood in all but 7. There was a definite color change in the colloidal gold solution in the luetic zone in every case except one. In the majority of instances the color change occurred up to No. 4. This is more marked than occurs in cerebrospinal lues, but not sufficiently characteristic to be of much diagnostic value between it and tabes. Case 83 had been previously treated with salvarsan intravenously, had Argyll-Robertson pupil, loss of knee-jerks, shooting pains, and loss of bladder control. Both the blood and spinal fluid findings were normal. However, under further antispecific treatment intraspinally (Swift and Ellis) his lightning pains stopped and his bladder improved. Case 9 gave a typical paretic curve in the colloidal gold solution, but no clinical evidence of paresis. In Case 63, where we have another typical paretic curve, the patient showed evidence of memory impairment, which makes the probable diagnosis one of taboparesis. In Cases 54 and 187 all findings were negative except colloidal gold precipitation in the syphilitic zone.

CEREBROSPINAL LUES—27 CASES.

Case No.	Wassermann.		Colloidal gold test.	Globulin.		Lymphocytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
2	0	+	1232100000	+	+	16	
7	+	+	1332100000	+	+	9	
8	0	0	1233220000	+	+	21	Positive history.
20	+	+	1332100000	+	+	6	
28	0	+	2343220000	+	+	38	
66	+	+	5555420000	+	+	116	Apoplexy; no mental symptoms.
72	+	+	1232210000	+	+	8	
73	+	+	0123431000	+	+	16	Postmortem, gumma of brain.
80	0	+	1332210000	+	+	3	
84	+	+	2343210000	+	+	29	Major epilepsy.
85	+	+	4323100000	+	+	16	
112	+	+	1133420000	+	+	38	
119	+	+	2234300000	+	+	6	
120	+	+	1234200000	+	+	19	
121	0	0	1333320000	+	+	8	Positive history; typical case.
134	+	+	0133210000	+	+	4	
135	+	+	1233210000	+	+	16	
145	+	+	0123310000	+	+	5	
149	+	+	1334310000	+	+	22	
158	+	+	0234210000	+	+	12	
160	+	+	0122100000	+	+	8	
168	+	+	4555432000	+	+	42	
189	+	+	0123210000	+	+	16	
190	+	+	1334310000	+	+	4	
194	+	+	3332100000	+	+	96	
199	+	+	2334320000	+	+	18	
207	+	+	4543100000	+	+	68	

In cerebrospinal lues (27 cases) the globulin test was positive in all; there was lymphocytosis in 17 cases; the Wassermann in the spinal fluid was negative twice and in the blood negative 5 times. In all cases the colloidal gold test gave color changes in the syphilitic zone. In 3 instances there was the typical paretic curve without any clinical evidence of paresis.

CONGENITAL LUES—4 CASES.

Case No.	Wassermann.		Colloidal gold test.	Globulin.		Lymphocytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
71	+	+	5555431000	+	+	38	Juvenile paresis.
174	0	0	0100000000	0	0	3	After vigorous treatment.
175	+	+	0122100000	+	+	18	Associated with epilepsy.
92	+	+	1111210000	+	+	not done	Primary optic atrophy.

Our 4 cases of congenital syphilis are too few to be of much value, except that they confirm Miller and Levy's conclusions, namely, that in the spinal fluid of congenital luetics the colloidal gold test shows nothing more definite in the majority of cases than the Wassermann. This is all the more interesting when one remembers there is a more positive Wassermann in congenital than acquired lues. In their conclusions, Miller and Levy state that the colloidal gold test has no advantage over known laboratory procedures in the diagnosis of congenital syphilis. However, Grulee and Moody, and also Johnston, in a recent publication, are not in accord with this.

MENINGITIS—11 CASES.

Case No.	Colloidal gold test.	Globulin.		Cell count.	Remarks.
		Nonne.	Noguchi.		
16	0001233110	++	++	96	Tubercles found in spinal fluid.
61	0002334100	++	++	116	Tubercles found in spinal fluid.
131	0133432110	++	++	286	Tuberculous meningitis postmortem.
152	0002333421	++	++	94	Tubercles found in spinal fluid.
162	0123322000	++	++	69	Tubercles found in spinal fluid.
203	0001221000	++	++	192	Clinical tuberculous meningitis.
105	0000133321	++	++	1260	Pneumococci found in spinal fluid.
108	0001234441	++	++	116	Pneumococci found in spinal fluid.
106	0022343111	++	++	492	Meningococci found in spinal fluid.
107	0013443200	++	++	612	Meningococci found in spinal fluid.
151	0000122100	++	++	1242	Meningococci found in spinal fluid.

In our meningitis cases (6 tuberculous, 2 pneumococcic, 3 meningococcic) all but two gave the characteristic "Verschiebung nach oben" in the colloidal gold test, namely, a decolorization in the

higher dilutions, but the zone effected or the intensity of the reaction was not constant. The reaction usually becomes more marked as the disease progresses. All gave a marked globulin test and a cell count ranging from 94 to 1242 per cubic millimeter.

CEREBROSPINAL LUES ASSOCIATED WITH PNEUMOCOCCIC MENINGITIS.[2]

Case No.	Wassermann.		Colloidal gold test.	Globulin.		Lymphocytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
221	+	+	1124300000	+	+	12	
223	not taken		1121134421	+	+	Many leukocytes	Diplococci pneumoniæ in spinal fluid.

A case of cerebrospinal lues with a subsequent pneumococcic meningitis gave the above findings. The variations in the colloidal gold curve were interesting. The pneumococcic meningitis developed one month after the cerebrospinal lues.

TETANUS—3 CASES.

Case No.	Colloidal gold test.	Globulin.		Lymphocytes.	Remarks.
		Nonne.	Noguchi.		
204[3]	0003343200	Trace	Trace	4	
205	0000244310	Trace	Trace	8	
206	3443221000	++	++	Many	Hemorrhagic fluid.

In 3 cases of tetanus the spinal fluid findings were interesting in that the colloidal gold curve showed "Verschiebung nach oben" similar to meningitis. However, the other findings were negative. The Wassermann examined in Case 204 was also negative.

ACUTE ANTERIOR POLIOMYELITIS—4 CASES.

Case No.	Colloidal gold test.	Globulin.		Lymphocytes.
		Nonne.	Noguchi.	
207	1233210000	0	0	6
208	0000110000	0	0	2
209	0000000000	0	0	0
210	0000000000	0	0	8

[2] Reported in full in Jour. Amer. Med. Assn., July 29, 1916.
[3] Wasserman in spinal fluid negative.

MISCELLANEOUS GROUP—76 CASES.

Case No.	Wassermann.		Colloidal gold test.	Globulin.		Lymphocytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
3	0	0	0000000000	0	0	6	Transverse myelitis.
1	0	0	0000000000	0	0	2	Hysteria major.
5	0	0	0000000000	0	0	0	Involutional melancholia.
14	0	0	0000000000	0	0	4	Syphilophobia.
17	0	0	0000123110	0	0	6	Spinal cord tumor.
21	0	0	0000000000	0	0	3	Epilepsy.
22	0	0	0000000000	0	0	0	"
23	0	0	0000000000	0	0	2	"
24	0	0	0000000000	0	0	4	"
25	0	0	0000000000	0	0	0	Friedreich's ataxia.
27	+	0	0000000000	0	0	2	Progressive muscular dystrophy.
43	0	0	0000000000	0	0	3	Manic depressive insanity.
44	0	0	0000000000	0	0	9	Manic depressive insanity.
45	0	0	0000000000	0	0	6	Manic depressive insanity.
46	0	0	0000000000	0	0	0	Manic depressive insanity.
47	0	0	0000000000	0	0	2	Manic depressive insanity.
48	0	0	0000000000	0	0	0	Manic depressive insanity.
49	0	0	0000000000	0	0	0	Manic depressive insanity.
50	0	0	0112100000	0	0	0	Manic depressive insanity.
51	0	0	0000000000	0	0	1	Manic depressive insanity.
52	..[4]	..[4]	0000000000	0	0	0	Manic depressive insanity.
53	0	0	0000000000	0	0	0	Manic depressive insanity.
56	0	0	0000000000	0	0	2	Familial spastic paralysis.
74	0	0	0000012220	0	0	6	Involutional melancholia.
75	0	0	5543100000	0	0	9	Multiple sclerosis.
110	0	0	0000000000	0	0	4	" "
212	0	0	0000000000	0	0	6	" "
216	0	0	0000000000	0	0	8	" "
76	0	0	0000000000	0	0	0	Mother of No. 71.
77	0	0	0000000000	0	0	2	Wife of No. 60.
78	0	0	0122220000	0	0	9	Sydenham's chorea.
79	0	0	0000000000	0	0	4	Huntington's chorea.
89	0	0	0000000000	0	0	6	Delirium tremens.
90	0	0	0112210000	0	0	8	" "
91	0	0	0111211000	0	0	5	" "
92	0	0	0000000000	0	0	4	" "
93	0	0	0112221000	0	0	2	" "
94	0	0	0000000000	0	0	3	" "
95	..[4]	0	0000000000	0	0	9	" "
96	0	0	0000000000	0	0	7	" "
97	0	0	0222100000	0	0	8	" "

[4] Not done.

MISCELLANEOUS GROUP—76 CASES.—*Continued.*

Case No.	Wassermann.		Colloidal gold test.	Globulin.		Lymphocytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
98	..[4]	..[4]	0000000000	0	0	1	Delirium tremens.
99	0	0	0000000000	0	0	3	" "
100	0	0	0000000000	0	0	0	" "
101	0	0	0000000000	0	0	2	" "
102	..[4]	..[4]	0000000000	0	0	0	" "
103	0	0	0000000000	0	0	6	" "
104	0	0	0000000000	0	0	0	" "
229	..[4]	..[5]	0112111000	+	+	..[4]	Fluid from cerebellar cyst.
113	0	0	0000000000	0	0	2	Acute alcoholism.
114	0	0	0000000000	0	0	0	" "
115	..[4]	0	0000000000	0	0	1	" "
116	..[4]	0	0000000000	0	0	3	" "
117	0	0	0000000000	0	0	0	" "
118	0	0	0000000000	0	0	2	Huntington's chorea.
127	0	0	0001223300	+	+	56	Spinal cord tumor.
128	0	0	0012100000	0	0	4	Dementia precox.
129	0	0	0000000000	0	0	2	Uremic convulsions.
130	0	0	0000000000	0	0	3	Syphilophobia.
132	0	0	0000000000	0	0	9	Cerebellar tumor.
133	0	0	0000000000	0	0	16	Meningismus.
137	0	0	0000000000	0	0	9	Acute mania.
138	..[4]	..[4]	0000000000	0	0	8	" "
141	0	0	0000000000	0	0	8	Uremia.
149	0	0	0000000000	0	0	83	Meningismus.
143	0	0	0112221000	0	0	4	Bell's palsy.
146	0	0	0000000000	0	0	2	Migraine.
148	0	0	0000000000	0	0	0	Trifacial neuralgia.
153	0	0	0122210000	0	0	12	Brain tumor.
157	0	0	0000000000	0	0	3	Myasthenia gravis.
159	0	0	0000000000	0	0	1	Brain tumor.
163	0	0	0000000000	0	0	4	Cerebral palsy of childhood.
166	0	0	0000000000	0	0	4	Bell's palsy.
172	0	0	0023455555	..	..	2	[6] ? ?
178	0	0	0000000000	0	0	0	Myasthenia gravis.
219	0	0	0000000000	0	0	2	Wife of tabetic.

Spinal fluids from acute anterior poliomyelitis gave nothing definite. All were obtained during the acute stage of the disease. One case (No. 207) gave a colloidal gold curve in the luetic zone. Johnston found this present in 4 cases during the acute stage. He subsequently examined 2 of these after acute symptoms had subsided and in both the colloidal gold curve was negative. He beleves that this occurrence of an early transitory reaction in the syphilitic zone in the acute stage of anterior poliomyelitis suggests an important aid in the diagnosis of this disease.

In our miscellaneous group (76 cases) all findings were practi-

[4] Not done.

[5] Transverse myelitis associated with Pott's disease; spinal fluid showed xanthochromia at three separate lumbar punctures.

cally normal. The Wassermann in the spinal fluid in all cases was negative. One blood gave a positive Wassermann, the cell count was normal except in 2 cases of meningismus, in 1 brain tumor and in 1 spinal cord tumor; the globulin test was negative in all but 1. The colloidal gold test showed nothing definite, except occasionally a slight decolorization in the lower dilutions. In 3 cases of multiple sclerosis all findings were negative, but in 1 case (No. 75) the colloidal gold test showed a typical paretic curve with a negative Wassermann test. Similar findings have been reported. Miller and his co-workers report 3 cases; Flesh observed this curve 6 times out of 8 cases examined. Kaplan found it only once in 18 cases; Oetiker reports 1 case. The presence of a "paretic curve" with the other spinal fluid findings negative might be of help in the diagnosis of suspected multiple sclerosis. Occasionally one sees a report of a "paretic curve" with normal spinal fluid findings in other conditions. Oetiker observed this in a case of puerperal eclampsia; Miller in a brain abscess and in a case of cirrhosis of the liver. Case 172 gave interesting findings. The spinal fluid was slightly hemorrhagic (old hemorrhage) and contained an excessive amount of globulin. The patient had an old Pott's disease of seventeen years' duration, and during the past few months gradually developed a transverse myelitis with a flaccid paralysis. Both spinal cord tumor cases (Nos. 17 and 127) gave a decolorization in the higher dilutions.

SPINAL FLUID FINDINGS AFTER TREATMENT, WHERE ALL TESTS SHOWED IMPROVEMENT.[6]

Case No.	Wassermann.		Colloidal gold test.	Globulin.		Lymphocytes.	Remarks.
	Blood.	Spinal fluid.		Nonne.	Noguchi.		
37	0	+	3321000000	0	0	4	Paresis.
9	0	0	1232100000	0	0	2	Tabes.
179	0	0	2231000000	0	0	3	"
193	0	0	0000000000	0	0	1	"
186	0	0	1223200000	0	0	7	"

The effects of antiluetic treatment on these tests have been variable. In the main our syphilitic cases have been treated with salvarsan, intravenously and intraspinally (Swift and Ellis method), combined with mercury. In all cases there has been a gradual reduction of the cell count to normal. In the majority of cases the globulin test has become normal while in some it remained slightly positive. In 21 cases of paresis, treated thoroughly, all but 2 gave a negative blood Wassermann. However, in the spinal fluid it persisted positive in every case. Out of 22 cases of tabes treated, 16, or 73 per cent., gave a negative Wassermann both in the blood

[6] For original findings refer to same case numbers in early part of this paper.

and spinal fluid. In only 5 instances of all antiluetic cases treated did we notice any change in the colloidal gold curve, and in only 1 case did the curve become normal.

SUMMARY. 1. The most constant finding in a pathological spinal fluid is a positive globulin. It is indicative of an inflammatory process, but is of no specific import.

2. Pathological cerebrospinal fluids usually show some lymphocytosis. However, the number may be normal. Fluids from cases of meningitis almost invariably give a high cell count.

3. As an index of pathological change in the cerebrospinal fluid the colloidal gold reaction is more delicate than any other test here employed.

4. Normal spinal fluid usually causes no reduction of the colloidal gold. A slight reduction in any of the dilutions is of no diagnostic import, and may occur in normal spinal fluids.

5. Cases of tabes and cerebrospinal lues gives a typical colloidal gold curve in the luetic zone. Although in tabes the intensity of the curve is usually greater, it is not sufficiently constant to be of diagnostic value between the two conditions.

6. In paresis the colloidal gold test is sufficiently frequent and characteristic to warrant the term "paretic curve," and is of great diagnostic value. However, it has been observed in cases of tabes, cerebrospinal lues, multiple sclerosis, brain abscess, and once in puerperal eclampsia.

7. In meningitis the colloidal gold curve usually occurs in the higher dilutions, and is probably of value in the diagnosis of doubtful cases.

8. In spinal fluids with normal findings, except a paretic colloidal gold curve in doubtful cases, the possibility of a multiple sclerosis must be strongly considered.

9. The colloidal gold test is more delicate than the Wassermann test. Spinal fluids from luetics have given a colloidal gold luetic curve with a negative Wassermann. However, we have never observed a normal colloidal gold curve with a positive Wassermann in the spinal fluid. Exceptions to this are the congenital luetics.

10. Under antiluetic treatment there is usually a reduction in the cell count and globulin of the spinal fluid; frequently the Wassermann becomes negative; rarely is there a change in the colloidal gold test.

11. No spinal fluid test (except the presence of bacteria) is specific. Every test is simply that much coöperative evidence and should be combined with the history of the case and the clinical findings.

I desire to express my appreciation to Dr. Leitch, pathologist at Mounds Park Sanitarium, and Dr. Barron, formerly pathologist at the City and County Hospital, for their kind help and interest in the study of our spinal fluids.

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CONCERNING THE CAUSATION OF EDEMA IN CHRONIC PARENCHYMATOUS NEPHRITIS: METHOD FOR ITS ALLEVIATION.[1]

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One of the most striking clinical manifestations of chronic parenchymatous nephritis is the development of edema or anasarca. Its occurrence is intimately associated with a diminished elimination of salts and water, believed to be due to a reduced power of the kidneys to excrete these substances. Those who have had occasion to observe the condition know well the severe proportions which it may assume, the distress which it causes the patient, and the inadequacy of medicinal treatment or the usual dietetic restrictions.

The present communication forms part of a larger study on nephritis begun a number of years ago. Its purpose is to put on record certain facts concerning the nature of the anasarca occurring in chronic parenchymatous nephritis which are of clinical importance and to suggest a new method of treatment which promises to be useful. The reason for selecting this particular phase of the subject is the conviction (gained in the study) that the edema, or anasarca, is one of the most important phenomena in the disease, and that by its alleviation and prevention great progress is made toward ultimate relief of the renal condition.

[1] Read before the Section on Medicine at the New York Academy of Medicine, October 17, 1916.

Ever since Bright's discovery of renal disease the opinion has prevailed that all the phenomena associated with it are attributable to the pathological changes and the disordered function of the kidneys. It is now conceded that the morbid manifestations of chronic parenchymatous nephritis differ from all other forms of renal disease. Its onset, progress, and duration, its tendency to subcutaneous and serous effusions, and the cardiovascular conditions and urinary findings—all differ from those observed in other varieties of renal disease. It is not the object, at present, to discuss the chemical and pathological features of chronic parenchymatous nephritis as a whole, but it is important to note (and the conclusion seems justifiable from the observations thus far made) that among the cases of parenchymatous nephritis there is a group with a constitutional disorder in which the renal and other manifestations are concomitant or secondary in point of development and importance.

Much discussion has been indulged in concerning the origin of edema in nephritis, and many theories have been propounded concerning the mode of its production.

Thus it was[2] believed that the edema was the result of a "hydremia" from the retention of water caused by the inability of the kidneys to excrete it. Cohnheim[3] supposed that the edema was brought about by an increased permeability of the capillary vessels, induced by the malnutrition or poisoning incidental to the nephritis, which permitted fluid to filter through into the subcutaneous tissues and serous cavities. The hypothesis which has received the soundest clinical confirmation, and still retains many adherents, is that of Widal[4] and his associates, which teaches that the kidneys in this disease have a deficient capacity to eliminate salt (sodium chlorid). The accumulation of salt in the body causes a retention of water, thus giving rise to the anasarca. Fischer's[5] view that the edema is due to an "acidosis" has not received confirmation.

These are the principal views concerning the production of effusions in the body in chronic parenchymatous nephritis. They all attribute the phenomenon in one way or another to the retention of water and salt caused by the inability of the kidneys to eliminate them adequately. The position of the kidney in the animal economy is such that alterations in renal function may result from causes outside the kidney, so that the retention of salt and water, with the consequent formation of edema, may be due to other factors than renal insufficiency. It is evident, of course, that no massive effusion could occur without a corresponding retention of fluid, but the cause need not reside in the kidneys.

[2] v. Noorden: Pathol. d. Stoffw., 1906, i, 1043.
[3] Allg. Path., 1880, ii, 432.
[4] Bull. et mém. Soc. méd. d. hôp. de Paris, 12 Juin, 1902.
[5] Nephritis, 1912.

Whereas it is undeniable that a state of hydremia of varying degree exists in chronic parenchymatous nephritis, just how such a condition can produce edema is not at all clear. In recent work Baehr and I[6] have found that in nephrectomized animals suffering from experimental diabetes a marked state of hydremia develops (increase of 70 per cent. in blood volume) without causing any edematous deposits. Concerning the view that increased permeability of the walls of the capillaries plays a part in the production of edema, it might be said that modern research indicates that the capillary vessels are less permeable to salt and water in renal disease than they are normally. Thus in the work of Chisholm,[7] Boycott and Douglas,[8] and more recently that of Bogert, Underhill and Mendel,[9] we find evidence that "the condition of nephritis produced experimentally 'effects an alteration in the permeability of the walls of the capillaries in such a way as to hinder the passage of fluid from the blood to the tissues.'" Widal's view that the retention of salt is directly and indirectly responsible for the production of edema would be valid on the basis of the evidence furnished were it not for the fact that numerous other affections of the kidneys also cause a retention of salt without ever leading to the development of edema. Other French observers[10] explain this discrepancy by assuming that the retained salt may exist in two states: one in firm combination with the tissue protoplasm—"chlorure fixé"—and the other, being free, "chlorure libre." The first phase gives rise to retention of salt without producing edema, "retention chlorure seche," the other phase leads directly to the retention of water, thus causing edema—"retention chlorure hydropigène." The explanation is ingenious but not convincing. Just why two such states for chloride retention should exist is not at all clear. One cannot deny Widal's observations on the effect of salt administration on the edema in chronic parenchymatous nephritis. That is as it should be. Neither can we gainsay the observation concerning hydremia and the retention of water. Least of all can we deny the fact that extreme forms of renal disease can exist, causing retention of different urinary substances without producing edema. Even total anuria of long duration may terminate and give no evidence of edema. Passler[11] records a case of anuria of eleven days' standing in which no edema developed.

It is evident, therefore, that more information is needed for the elucidation of this perplexing phenomenon. Some knowledge is gained by a comprehensive study of the blood sera and the effusions, particularly in the light of the newer physicochemical principles.

[6] Epstein, A. A., and Baehr, G.: Jour. Biol. Chem., 1916, xxiv, 1.
[7] Jour. Path. and Bacteriol., 1914, xix, 265. [8] Ibid., 221.
[9] Am. Jour. Physiol., 1916, xli, 189.
[10] Marie, R.: Semaine méd., 1903, p. 385.
[11] Deutsch. Arch. f. klin. Med., 1906, lxxxvii, 569.

In 1912–1914[12] I published a series of papers recording the results of chemical studies upon blood sera and puncture fluids. The aim of these studies was to ascertain the various changes which the blood undergoes in different types of disease, particularly in respect to the proteins. Whereas no final deductions were drawn then from the variations encountered, certain points were definitely emphasized. It was observed that the proteins of the serum are subject to extensive variations. Whereas normally the blood serum contains 6 to 8 gms. of protein to the 100 c.c., of which a little more than one-third is globulin; in disease the quantity of protein may be very much reduced but the globulins may show both a relative and absolute increase. In the serum of cases of chronic parenchymatous nephritis the protein content shows the greatest reduction; whereas the increase in globulin content is most pronounced, and it may constitute nearly all of the protein present. (See Table I.)

TABLE I.—AVERAGE COMPOSITION OF BLOOD SERA. GRAMS PER 100 C.C.

	Total protein.	Globulin.	Albumin.	Globulin per cent.
Normal	7.400	2.738	4.662	37.0
Cardiac conditions	6.408	2.240	4.417	33.9
Chronic interstitial nephritis	6.704	2.396	4.310	35.7
Chronic parenchymatous nephritis	3.928	3.462	0.466	89.2

TABLE II.—AVERAGE COMPOSITION OF EFFUSION FLUIDS. SEROUS FLUIDS.

Cardiac conditions	3.352	1.199	1.788	43.0
Hepatic cirrhosis	3.174	1.318	1.856	41.0
Chronic parenchymatous nephritis	0.285	0.285	0	100.0
SUBCUTANEOUS FLUIDS.				
Chronic parenchymatous nephritis	0.098	0.080	0.018	81.0

For reasons which will be given in a future communication I am of the opinion that some of the changes occurring in the proteins of the serum, more especially the globulin content, are the result of well-defined influences acting upon the blood. In contrasting the findings in the sera of patients with different forms of renal disease the conclusion has been reached that chronic parenchymatous nephritis is genetically different from all other forms and that the change in the protein composition plays a direct part in the production of some of its clinical manifestations, particularly that of edema.[13] From a broad, clinical stand-point the cases of renal disease studied may be grouped into three classes.

[12] Epstein, A. A.: Jour. Exper. Med., 1912, xvi, 719; 1913, xvii, 444; 1914, xx, 334.
[13] Ibid., 1914, xx, 334.

1. The cases of chronic interstitial nephritis show no change from the normal in the character of the protein composition of the serum, nor in the ratio which the individual fractions bear to each other. On the other hand, the incoagulable and non-protein N of the serum show marked fluctuations, some of which correspond to the degree of functional deficiency of the kidneys.

2. In cases of localized disease of the kidneys (surgical conditions) the changes in the blood serum are twofold: One concerns the protein and is traceable to infections; the other concerns the non-protein constituents and varies with the amount of destruction of the kidney substance. When infection is present an increase in the globulins is observed similar to that occurring in infections in other localities; the non-protein N increases apparently in direct proportion to the degree of deficiency of the kidney.

3. In cases of chronic parenchymatous nephritis the amount of protein in the blood is markedly diminished. From the evidence which we possess the cause of the diminution of the amount of protein is ascribable largely if not entirely to the loss of protein in the urine. The amount of protein lost in the urine daily may be insignificant, and if immediately replaced may exert no influence on the content of the blood serum. As a rule, however, the loss is very considerable.

Dieballa and von Kétly[14] record a protein output in the urine of 24 gms. I have had occasion to observe an albuminuria of several months' duration, with a daily output of protein ranging from 18.5 to 26.2 gms. Now if we remember that the total protein in the blood averages only about 210 gms. the daily loss of so much protein eventually causes a tremendous drain upon the blood serum unless the deficit is replaced. Under normal conditions the loss of fluid from the blood (hemorrhage or otherwise) is immediately replaced by the passage of fluid from the tissue spaces back into the blood capillaries. The experiments of Turner, Marshall and Lamson[15] and their associates on plasmapharesis (*i. e.*, removal of plasma from the blood) show that the protein content of the serum gradually diminishes under such conditions.

In the nephritic individual the loss incurred may at first be covered so that no diminution in the blood-serum proteins may be evident; but as the disease progresses and the albuminuria becomes more intense the loss may exceed the amount restored, so that finally impoverishment of the serum in proteins results. As a rule the nutritional condition of the patients and the dietetic restrictions to which they are subjected in the course of treatment favor such a development.

The fact is that in chronic parenchymatous nephritis the quantity

[14] Dieballa and v. Kétly: Deutsch. Arch. f. klin. Med., 1898, lxi, 761.
[15] Jour. Pharmacol., 1915, vii, 129.

of protein in the serum is diminished. The decrease appears to be proportional to the intensity and duration of the disease. The reduction in the proten content of the serum is not due to the hydremia. The work of Dieballa and von Kétly[16] furnishes proof of that.

Neither is the diminution in the content of the serum protein to be ascribed to a migration of the substance through the capillary walls into the tissue spaces. Chemical analysis of the edema fluids in the pure forms of chronic parenchymatous nephritis (by that I mean instances of the disease without cardiovascular involvement) shows that they are made up principally of salts and water.[17] The protein content is trifling. The conclusion is therefore unavoidable that the decrease in the protein content of the serum in these cases is to be attributed chiefly to the loss of protein in the urine. But what relation does this bear to the production of edema?

In order to comprehend fully the nature of the processes which are active in the production of edema it is necessary to consider for a moment the manner in which the exchange of fluid between the blood and the tissues is regulated.

As stated before the loss of fluid from the blood is rapidly restored by the passage of fluid from the tissue spaces back into the blood capillaries. Two theories have been advanced to explain this absorption of fluid: (1) the backward filtration theory of Landerer, and (2) the osmotic theory of Starling. According to the first theory, when the pressure in the capillaries falls below that in the tissue spaces the fluid is forced back into the capillaries. When the reverse occurs, fluid passes from the capillaries to the tissue spaces. According to Starling there is normally a balance in the production and absorption of tissue fluid between the filtration pressure in the capillaries and the osmotic pressure of the colloids of the blood and tissue fluid.

Plasma and tissue fluid are practically identical in everything except protein. Starling[18] showed that the blood proteins exert an osmotic pressure of about 4 mms. of mercury for every 1 per cent. of protein. Normally the plasma contains more protein than the tissue fluid; so that normally an equilibrium is maintained in the to-and-fro movement of fluid by capillary pressure working from the vessels in the direction of the tissues and the osmotic pressure of of the blood colloids acting in the reverse direction. Usually the osmotic pressure of the blood is greater than that of the tissue fluid because of the greater amount of colloids, and, as a result of this influence, the direction of flow is from the tissues to the blood capillary system. The effect of the two operating forces is naturally different. The one, capillary pressure or backward filtration (which is the active force in restoring blood volume after hemorrhage, etc.), must cause the passage of fluid which is approximately of the same

[16] Loc. cit. [17] Epstein, A. A.: Jour. Exper. Med., 1914, xx, 334.
[18] Quoted from F. H. Scott, Jour. Physiol., 1916, l, 157.

composition as that contained at the source. For example if transudation occurs because of increased capillary pressure the migrating fluid must be like that of the blood serum. This is verified by the composition of effusions encountered in conditions of static disturbances, such as cardiac disturbances, cirrhosis of the liver, etc. (See Table II.) When the capillary pressure is lessened (as after hemorrhage) the composition of the fluid which passes from the tissues into the blood stream must be like that of the tissue fluid. Scott[19] in the study of this subject has shown that the fluid which passes from the tissues under these conditions contains from 0.6 to 2.09 per cent. of protein.

On the other hand, the fluid which passes in response to the osmotic pressure of colloids should be practically a solution of salts. Analysis of the edema fluid encountered in cases of chronic parenchymatous nephritis shows the composition to be one of salts and water. (See Table II.) The protein content is insignificant and may be derived from the fluid of the tissue spaces.

We have in these considerations a set of facts which dovetail and afford us a starting-point for the comprehension of the mechanism which leads to the production of edema. It is recognized on the one hand that the blood serum normally contains more protein, *i. e.*, more colloid material than the tissue fluid, and that by virtue of this predominence it possesses a greater osmotic pressure which is vital in maintaining a balance in the exchange of fluid between the blood and the tissues. The examination of the blood sera in cases of chronic parenchymatous nephritis reveals the fact that the protein, *i. e.*, the colloid content, is very much reduced, a loss sometimes equivalent to 60 or 70 per cent. and more of the total serum protein. In terms of osmosis this loss of protein represents a pressure equal to 20 to 24 mms. of mercury, a factor sufficient to disturb the equilibrium in the exchange of fluid between the blood and the tissues. More precisely the deficit in serum protein causes a fall in the osmotic pressure of the blood. This disturbance does not only favor the passage of fluid from the blood to the tissues, but also gives to the tissues the controlling power to absorb and retain fluid.

From the very nature of the force which is concerned in the process (namely, that of osmosis) the fluid which passes from the blood to the tissues must be a solution of salts. The fluids which we find in the effusions in chronic parenchymatous nephritis are practically such solutions. (See Table II.) As pointed out before, the protein content is negligible and may not be derived from the blood.

The hypothesis for the production of edema in chronic parenchymatous nephritis which I therefore propose is briefly as follows: The loss of protein incurred by the blood serum through the continuous albuminuria causes a decrease in the osmotic pressure of the

[19] Jour. Physiol., 1916, l, 157.

blood, which fact favors the absorption or imbibition and retention of fluid by the tissues. This conclusion gains support from the experiments performed by Tullio Gayda,[20] who found that the edema which is produced in perfusion experiments when normal saline or Ringer solution is used is prevented by the addition to the perfusing fluid of colloids which are in osmotic equilibrium with the colloids of the lymph and tissues. This may not be the only factor but it is an important one.[21] Other evidence is also available to confirm this view, but space will not permit of elaborating further upon this phase of the subject. Suffice it to say that through a change in the protein composition of the blood plasma a condition is produced which is capable of causing the retention of fluid in the tissues.

Certain other factors which are important in the chemical and physical pathology of the disease must be touched upon, as they enter largely into a consideration of the treatment. Whether it be that a state of malnutrition results from the impoverishment of the blood in proteins or that the diseased condition, commonly termed chronic parenchymatous nephritis, is genetically a disorder of nutrition, we find in the blood definite evidence of tissue starvation. The evidence which I have in mind is the remarkable increase in the lipoid content of the blood. A number of such observations are on record. Thus Chaufford, Rechit and Grigaut[22] have noted an increase in the lipoid content. Recently I had occasion to observe very unusual amounts of lipoid substances in the blood serum of cases of parenchymatous nephritis. (See Table III.) The ac-

TABLE III.—CHOLESTERIN CONTENT OF BLOOD SERA. MILLIGRAMS PER 100 C.C.

Diagnosis.	Cases.	Average.	High.	Low.
Chronic interstitial nephritis	24	174	265	100
Uremia	5	133	194	87
Arteriosclerosis	7	163	218	100
Cardiac conditions	19	157	294	104
Bichloride poisoning	2	127	130	125
Chronic parenchymatous nephritis	9	559	1230	333

cumulation of these substances in the blood probably arises partly from the mobilization of fat deposits from the subcutaneous tissues and other sources and to a large extent perhaps from degenerative processes in the tissues. The cause of fat mobilization when a lipemia develops may be partly physical displacement, due to the effusions. Usually, however, the condition in the blood is one of

[20] Arch. Sc. Med., 1916, xxxix, 389.

[21] The increase in the globulin content of the blood serum, and the excessive accumulation of lipoids, constitute additional factors which contribute to the causation of edema in chronic parenchymatous nephritis, and interfere with the elimination of salt and water by the kidneys.

[22] Compt. rend. Soc. de biol., 1911, p. 317.

lipoidemia, thus pointing to a metabolic derangement similar to that observed in starvation in advanced diabetes and in pellagra. The degree of nutritional disturbance and fat mobilization can be appreciated only after the cases begin to improve and the edema subsides. Then the patients manifest very marked wasting.

The increase in the lipoid content of the blood is important not only because it gives evidence of a grave nurtitional disturbance but also because it affects the pathology of the disease in other ways. Kaethe Dewey[23] has recently shown that the mere presence of excessive amounts of cholesterin in the blood is capable of producing definite pathological lesions in the kidneys and perhaps also affecting their function. From the work of Mathilde Koch and Carl Voegtlin[24] and also that of Herlizka[25] and Gayda[26] it appears that abstractions of lipoids from tissue cells cause imbibition of fluid with consequent swelling of the cells.

The problem in the treatment of edema in chronic parenchymatous nephritis is to relieve the condition and prevent its recurrence. The mere removal of effusion fluid by paracentesis and puncture, if feasible, may relieve it partly, but does not, as a rule, prevent a reaccumulation. I need not dwell upon the medicinal means used to promote renal activity. The failure of such procedures to influence the edema is classic. It has been shown repeatedly that the kidneys in this type of disease are capable of eliminating the different urinary substances. Their inability to excrete sufficient salt and water is due to causes outside of them.

On the basis of the views presented concerning the causation of edema the real problem in its treatment is the restoration of normal conditions in the blood and the establishment of a healthy state of nutrition. The blood in these cases, as previously stated, shows a marked decrease in protein and an increase in lipoids. The indications are: (1) to increase the protein content of the blood and thus help it regain its normal osmotic power, and (2) to remove or cause the reabsorption by the tissues of the excessive lipoids. The restoration of the protein content may be accomplished by two methods: (1) Massive infusion or transfusion of healthy blood accompanied by the removal of equal quantities of blood from the patient. The latter procedure is necessary to accommodate the introduction of additional blood so as not to embarrass the circulation. It also serves to remove some of the excessive lipoids. (2) Most important is the proper administration of a high protein and fat-poor diet.

The employment of transfusion is undoubtedly helpful and affords a good start in the treatment, but, of course, is not always feasible

[23] Arch. Int. Med., 1916, xvii, 757.
[24] Bull. Hyg. Lab., 1916, No. 103, p. 129.
[25] Arch. di Fisiol., 1909, vi, 369.
[26] Loc. cit.

for obvious reasons. It must be remembered also that whereas the replacement of the impoverished blood of the patient with healthy blood helps toward the restoration of normal conditions, the effect is necessarily only a temporary one, for the continuation of the albuminuria causes a constant loss of blood protein. Chief reliance must therefore be placed upon adequate dietetic measures. The method consists, therefore, in the administration of large quantities of properly selected proteins with a minimum of carbohydrates and the exclusion of fats. The reason for restricting the carbohydrates is twofold: (1) to promote a maximum assimilation of protein, and (2) to exclude the greater production and retention of water which is incidental in the metabolism of carbohydrates. The fats are excluded because of the marked increase of fatty substances in the blood.

DIET EMPLOYED.

	Daily amount.
Food value	1280 to 2500 calories
Proteins	120 to 240 grams
Fats (unavoidable)	20 to 40 "
Carbohydrates	150 to 300 "

ARTICLES USED.

Lean veal, lean ham, whites of eggs, oysters, gelatin, lima beans, lentils, split peas, green peas, mushrooms, rice, oatmeal, bananas, skimmed milk, coffee, tea and cocoa.

As for the administration of fluids and salts, I might say that the fluid allowed is restricted to the quantity present in the food, plus that which is necessary for the comfort of the individual patient, amounting usually to 1200 to 1500 c.c. The amount of salt allowed is the quantity sufficient to make the food palatable.

The method is necessarily slow and requires persistence, but its effect is indeed very salutary. The protein content of the blood increases and the lipoidemia subsides. Accompanying these changes in the blood there is a progressive increase in the excretion of urine with a gradual disappearance of the edema. The albuminuria also diminishes and the patient's health improves steadily.

The diet listed above is relatively low in calories; other articles of food are added gradually as conditions allow. The fats are restricted so long as the lipoid content in the blood remains elevated.

The number of cases treated thus far is not large, but such of them as we had represented extreme types of the disease. The results obtained have been very encouraging. A detailed report of these cases will be published later.

THE COMPLEMENT-FIXATION TEST IN THE DIAGNOSIS OF TUBERCULOSIS, WITH A STUDY OF 135 CASES.

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The early diagnosis of tuberculosis, or perhaps, more correctly speaking, the determination of the clinical importance of the foci which most of us are supposed to harbor, is admittedly one of the most difficult as well as most important problems in clinical medicine. So many factors have to be considered, and in certain types of cases all the available data are so indefinite, that sometimes the best we can do is to make a more or less accurate guess.

I cannot agree with those who consider the subcutaneous injection of old tuberculin, hitherto the most reliable biological test, an entirely safe procedure. If the injections are given in doses so small that no deleterious effect can be produced, we may fail in clinically active cases to get a definitely recognizable reaction, and then if repeated doses are increased very slowly, immunization may occur. This is what happens with increasing therapeutic doses. Whenever a reaction does occur there is at least a transient lowering of resistance to the infecting germ. This corresponds to Wright's "negative phase," during which phagocytic power, as shown by the opsonic index (and therefore the immunity mechanism of the body), is more or less weakened. Now, in a large proportion of suspected cases this is probably quite unimportant, because it is succeeded by a strongly positive phase. In a smaller group, however, definite harm may be produced. In a patient with a fairly low resistance, for example, and with a focus which is moderately active, the transient lowering of resistance occurring as a result of the subcutaneous test may cause increased activation of the focus, and such an event might easily turn the scale against the patient. This may not be at all obvious at the time, and, in fact, probably would not be, but might manifest itself by later clinical developments, the relationship of which to the tuberculin test might not be suspected.

I am quite well aware that many eminent clinicians, Osler among them, have declared for the harmlessness of the tuberculin test carefully employed. The biological facts above set forth are, however, indisputable, and the conclusion that positive harm might result seems unavoidable. In fact I believe I have seen such results follow its diagnostic use. Klebs[1] says that when carefully used in proper doses and in "properly selected" cases it is free from harmful effects, but adds that it should never be resorted to until

[1] Tuberculosis, 1909, p. 339.

all other means have failed. Certainly these are peculiar limitations with which to surround a perfectly safe diagnostic procedure. Lawrason Brown[2] in discussing the therapeutic use of tuberculin appears to offer a plausible explanation of the way in which the anaphylaxis occurs, and the same explanation would seem to apply to the harmful results which might follow its diagnostic use. He says: "The immunity mechanism seems so adjusted that whatever primary protein escapes from the focus (tubercular) is immediately disintegrated; that is, the lytic process set up by the complement is so active that anaphylatoxin is never formed and the lysis carries the splitting process on to the formation of simpler bodies. Now, when a sufficient amount, however small, of tuberculin (primary protein) is injected into the body it changes this favorable balance and the action is not carried on so far, and anaphylatoxin results. To stem these anaphylatoxins is at times difficult and their result is disastrous."

The reaction to the diagnostic dose of tuberculin given subcutaneously is undoubtedly an anaphylactic phenomenon. The patient may practically always "stem" the results, but whether he emerges from the anaphylactic storm of the tuberculin reaction with benefit or harm is difficult to determine; but if the cases are not *properly selected*, a process which may require expert judgment, the result may be "disastrous." If a strongly positive opsonic phase follows the negative phase of the reaction, a result which we are aiming at in our therapeutic use of tuberculin, which I heartily approve, then the patient may be actually benefited by the tuberculin test. This reaction corresponds to a therapeutic overdose which we consider objectionable and always try to avoid. It is only when the anaphylactic shock is too prolonged and the opsonic power of the plasma too greatly lowered that the germs may take advantage of the situation to the detriment of the patient.

Aside from the question of the possible hazards of the tuberculin test, what dependence can be placed upon it? If positive, can we confidently assume that the patient has clinical tuberculosis? If it is negative, can we exclude it? The answer to both of these questions is no. Simon[3] says that from 90 to 100 per cent. of the cases of pulmonary tuberculosis give a positive reaction, while 92 per cent. of suspected cases and 56 per cent. of non-suspected cases give positive reactions. The percentage of positive reactions among cases of clinical tuberculosis is undoubtedly very large, but at least it may fail with lowered resistance, and in the very large group of cases, perhaps only moderately advanced, but with fever, either slight or severe, it certainly cannot be used. On the other hand, if 56 per cent. or even 25 per cent. of non-suspected cases give a reaction, though I am inclined to think that this is a rather

[2] Am. Jour. Med. Sc., 1912, cxliii, 527.
[3] Infection, Immunity, etc., p. 333.

high estimate, it certainly cannot be depended upon to prove the existence of clinical tuberculosis. The work of Otis, Bandilier and Roepke[4] seems to show that syphilis, in at least its early stages, may give rise to a positive reaction. This is especially important in view of the number of "cross-fixations" which sometimes occur in these two diseases. Independently of positive reactions in cases of syphilis, it may be fairly assumed that a large proportion of the positive reactions occurring in non-suspected cases, either in healthy individuals or those suffering from other diseases, are due to concealed foci, which may be pathologically active but clinically entirely latent. In brief, we find that the subcutaneous tuberculin test is not positive in all cases of active tuberculosis; is entirely inapplicable in the febrile state; habitually disappears in the cachectic state of late tuberculosis; and is not infrequently positive in cases in which no focus can be discovered and which are never known neither before nor after the test to show clinical manifestations of tuberculosis.

We naturally turn therefore with interest, but with not a little habitual distrust, to the complement-fixation test now on trial in the diagnosis of clinical tuberculosis, which is the main subject of this paper. This test has apparently arrived at the point where it offers much of hope without subjecting the patient to the hazards, however remote, of the subcutaneous tuberculin test. The biological basis upon which the tuberculosis complement-fixation is said to rest is substantially the same as in the case of the Wassermann test. There is, however, this difference: complement-fixation in the Wassermann test depends upon the presence of lipoid bodies, which are not at all specific for syphilis but are found in all the trypanosome diseases, and may even be produced by a meal very rich in fats, although in this latitude and with proper precautions no difficulties arise. In the tuberculosis complement-fixation test, however, the complement is said to be bound by an antibody which is absolutely specific and which is produced by the antigenic effect of the tubercle bacilli toxin. It was shown, for instance, by Citron that complement-binding antibodies were found in the blood of normal individuals after the injection of tuberculin. This is presumably the mechanism of the production of complement-binding antibodies in clinical tuberculosis by a process of auto-inoculation. Whether these antibodies will be found at any particular time or not will depend upon two factors: (1) whether toxic bacillary products are at that moment being, or have rather recently been, thrown into the blood from the tubercular foci, and (2) whether there is on the part of the organism an immunity response to the antigenic influence of these toxic bodies. Citron found that the presence of these complement-binding antibodies following the

[4] Klebs, T. B.: p. 340.

injection of tuberculin was transitory, and this is precisely what occurs in clinical cases. I have seen a case show 50 to 75 per cent. inhibition of hemolysis in one test and none in a second test made a week later. This is not at all peculiar to tuberculosis complement-fixation. The same thing has been observed in both the Neisser and Wassermann-fixation tests. It is well known that a single negative Wassermann does not exclude syphilis, although we do not therefore reject the Wassermann test as an aid in diagnosis.

As with the Wassermann so with the tuberculosis complement-fixation test, the results appear to depend somewhat upon the antigen used. A considerable number and variety of antigens have been used during the past six years, which is the period covered by these investigations. The antigens are classified by Miller[5] in a recent communication into four groups as follows:

Group I. Bacillary suspensions (which includes that used by Miller).

Group II. Tuberculins or filtrates (which includes Besredka's and Craig's antigens, and with which Bronfenbrenner's work has been done, as well as my own).

Group III. Bacillary extracts (used by Calmette and Masol, Much, Stimson and others).

Group IV. Tissue antigens (used by Bierbaum, Wolff, Eisner), these being analogous, of course, to alcoholic extract of the luetic liver in the Wassermann test.

Craig[6] using a filtrate antigen, made the test upon 166 cases of pulmonary tuberculosis, together with (for control purposes) 150 syphilitics, 100 patients suffering from other diseases and 100 normal individuals. Only two of the last three groups gave a positive reaction with the test. Of the 166 cases of pulmonary tuberculosis, 142 were positive and 24 negative; 107 of these cases were clinically active, giving 103, or 95 per cent., positive. Of the 59 inactive cases, 39, or 66 per cent. were positive. He found sometimes that the same case would give positive and negative tests on different days.

Bronfenbrenner,[7] using Besredka's antigen, studied 625 unselected hospital cases, with special reference to the association of syphilis and tuberculosis in those cases in which both of these diseases were clinically recognized or the patient gave both complement-fixation tests. Included in this 625 cases there were 174 cases of tuberculosis, 65 of which were active. Of the latter, 61, or 94 per cent. gave positive tuberculosis complement-fixation tests while 4 cases were negative. There were 27 cases of tuberculosis apparently undergoing recovery, of which 15 were positive and 12 negative.

There were 108 cases out of the 625 in which a clinical diagnosis

[5] Jour. Lab. and Clin. Med., August, 1916, p. 816.
[6] Am. Jour. Med. Sc., 1915, xl.
[7] Arch. Int. Med., 1914, xiv, 787.

of syphilis was made; 41, or 38 per cent. of these gave a positive tuberculosis complement-fixation test. This is undoubtedly a very large percentage of tuberculosis among syphilitics, and fairly raised the question as to the specificity of the serum test. By a carefully conducted series of experiments, which appear to me thoroughly convincing, he has proved that the two existing positive tests when associated are due to entirely distinct and separate antibodies. He shows very clearly that the tuberculosis complement-fixation reaction is not lipotropic in character. He removes the lipoid substances from the Besredka antigen by extraction with ether without impairing its complement-binding power. He then exhausts the tubercular antibodies by repeated fixations with Besredka's antigen, leaving the Wassermann reaction unimpaired, and then, of course, in another specimen of serum exhausts the syphilitic antibodies by suitable antigens, leaving the tuberculosis complement-fixation test unimpaired. His conclusion that the tuberculosis complement-fixation test is entirely specific, and that the individual giving positive fixation of complement with both this and the Wassermann test has both tuberculosis and syphilis, seems entirely justifiable. We are dealing with two of the most common and most serious infectious diseases, either one of which usually lasts through a long period of years, naturally predisposing to any other infection, and therefore it is not strange that a large proportion of syphilitics should be tubercular, and perhaps the reverse is almost equally plausible, owing to the widespread distribution of syphilis.

Miller,[8] using an antigen prepared by grinding tubercle bacilli with table salt and then adding water up to isotonicity, obtained 229 (98 per cent.) positive complement-fixation tests out of 232 clinically active cases, all of which had tubercle bacilli in the sputum. In 90 inactive or healed cases he found a negative reaction in 83 (7 were positive, and in 5 of these tubercle bacilli had recently been found in their sputum). In 140 cases in which the diagnosis was doubtful 32 gave a positive tuberculosis complement-fixation test. In 45 cases giving the positive Wassermann reaction, unlike Bronfenbrenner, he found only 2 with positive tuberculosis complement-fixation—in one of these the diagnosis of both syphilis and tuberculosis was subsequently established.

It was my intention to have this test made in my clinical laboratory with both the Wassermann and Neisser complement-fixation tests in practically every case, in order to get as broad a view-point of its clinical application as possible in both a positive and negative way. For various reasons this was not fully realized, but during the past year 135 complement-fixation tests have been made. While the number is not large the cases, for the most part, were

[8] Jour. Lab. and Clin. Med., August, 1916, p. 816.

very carefully studied, and it seemed that their analysis, with a brief review of and comparison with other recent work and my own conclusions based thereon, might be of sufficient interest to warrant its presentation.

Craig's antigen and an antihuman amboceptor derived from the rabbit were used in all the work, and the technic employed was that of Noguchi, simply substituting one antigen for another, or using several antigens with the same serum.[9]

For reasons which appear sufficient, clinical importance was attached to smaller degrees of inhibition than with the Wassermann test. If approximately 25 per cent. of inhibition occurred, or even less with perfect hemolysis in the serum control, it was regarded as significant and followed up by further investigation, because the complement-binding antibodies, unlike those in the Wassermann test, are specific. Of these 135 cases, 36 were regarded as cases of tuberculosis upon clinical grounds. In 22 tubercle bacilli had not been found, while they had been demonstrated in 14. Of the 22 with no bacilli present, 18 (or 77 per cent.) gave a positive complement-fixation test and 4 negative, while of the 14 cases with bacilli, 10 (or 71 per cent.) gave a positive and 4 a negative result.

There were 8 cases regarded as simply suspicious. Of these, 2 gave a positive complement-fixation and 6 a negative.

Nine cases, so far as could be determined, were normal in every respect. Of these 1 was positive and 8 negative. The one case giving a positive fixation, and supposed to be perfectly healthy, developed clinical tuberculosis within two or three months, which is now progressing. One other case in this group was regarded with suspicion, but gave a negative result and remains well.

Seventy-four cases were suffering from other diseases but were without suspicion of tuberculosis. Of these, 15 gave a positive and 59 a negative complement-fixation test.

The subcutaneous tuberculin test was made 16 times in the 135 cases. It was positive 4 times and negative 12 times. The 4 cases giving a positive tuberculin reaction all gave positive complement-fixation tests. Of the 12 cases in which the subcutaneous test was negative, 9 gave a negative complement-fixation test and 2 positive; one was positive at one time and negative at another.

In regard to the very interesting question of "cross-fixation" with the Wassermann test, my results are perhaps somewhat more discouraging than Bronfenbrenner's. In 95 cases both tests were made. There were 25 positive Wassermanns in the total of 95. Of these, 11 (or 44 per cent.) gave a positive tuberculosis complement-fixation test. This is 6 per cent. higher than that obtained in Bronfenbrenner's cases. In this connection it might be remarked that of the 11 cases with positive Wassermanns which also gave

[9] Am. Jour. Med. Sc., 1915, p. 150.

positive tuberculosis complement-fixation tests in 2 the clinical evidence was in favor of tuberculosis and in 9 against it. In two or three tuberculosis was plausible and in the remainder very improbable. Of the 70 with negative Wassermann, 20 gave positive tuberculosis tests or 28 per cent. as against 44 per cent. of those with a positive Wassermann. Of the cases with a positive tuberculosis complement-fixation test in which also the Wassermann was made, 31 in number, 11 (or 35 per cent.) had positive Wassermanns.

The results obtained by Miller with the bacillary suspension and by Bronfenbrenner with the tuberculin type differ remarkably in the "cross-fixation" obtained in cases with a positive Wassermann. In 45 cases of Miller's giving a positive Wassermann, 2 gave a positive tuberculosis complement-fixation, while Bronfenbrenner found in 108 cases of syphilis in which tuberculosis was not suspected, 41 cases (or 38 per cent.) giving positive tuberculosis complement-fixation. On the other hand, Craig, using an antigen of the same type as Bronfenbrenner, with some difference in the technic of preparation did not get a single positive tuberculosis complement-fixation in 150 cases showing a positive Wassermann. These discrepancies are somewhat difficult to reconcile. In both Craig's and Miller's cases of syphilis the percentage of cases giving positive tuberculosis complement-fixation is smaller than the actual number of cases one would expect to find in such a group, while in Bronfenbrenner's and in my own it is undoubtedly very large.

What then is the real clinical value of the tuberculosis complement-fixation test? As indicated at the outset the real problem is not to determine the presence or absence of tubercular foci in any part of the organism but the clinical importance of such foci. We content ourselves by classifying the cases as active and inactive. Let us inquire just what we mean by these terms. Obviously the question of activity may be considered from either a pathological or clinical view-point, the latter always including the former. The case is clinically active only when it is manifested by symptoms or signs, or both. In the absence of clinical manifestations a tubercular focus may be mildly active without disturbing its host, or even entirely quiescent, but the tubercle bacilli are still viable and capable of renewed activity under favorable conditions. Between the foci which are pathologically completely quiescent and those which are producing more or less severe clinical manifestations there must be a group of "border-line" cases which might readily pass into one or the other of these classes, *i. e.*, active or inactive, and which clinical observation and the autopsy room prove to us do actually migrate back and forth perhaps many times. The criteria heretofore available for gauging the clinical status of the "border-line" case have been unsatisfactory. The presence even of tubercle bacilli in the sputum only proves that a focus which indeed may be very small and producing no constitutional

disturbance, and would be entirely unrecognizable but for these bacilli, is discharging its contents into a bronchial tube. Such a focus might or might not pour toxins into the circulation, and upon whether it does so or not would naturally depend the presence or absence in the blood of complement-binding or other tubercular antibodies. The absence of tubercle bacilli from the sputum is equally inconclusive. The same thing may be said of the subcutaneous tuberculin test. Physical signs also fail us because they are not always recognizable when most needed and they may be obtained in a healed or rapidly healing focus. In view of all these facts and the demonstrable inconstancy of tuberculosis complement-binding antibodies, what can be reasonably expected from the complement-fixation test? While I believe that this test has arrived at the stage of clinical usefulness, yet its limitations are clearly defined. The absurdity of basing a clinical diagnosis upon any single laboratory test must be obvious to anyone upon the slightest reflection. This may be unfortunate, but in spite of these limitations the clinician should accept the information which it gives at its face value and make it a part, but only a part, of the basis of his clinical judgment. Viewed in this, its proper light, my own conviction is that with either the Besredka, Craig, or Miller antigen it is probably as reliable as and much more widely applicable than the subcutaneous test without the hazards of the latter. The positive complement-fixation obtained in unselected cases with varying pathology probably represents the "border-line" cases above referred to. Bronfenbrenner found 8 per cent. of 75 such cases giving positive fixation. In my own series of 65 such cases, 13 (or 20 per cent.) gave a positive complement-fixation test. My own results in this class of cases were in remarkable contrast to those of Craig, using presumably the same antigen. My own antigen was not made by Craig, however, but in one of our large biological laboratories,[10] and it may have varied slightly from Craig's formula; and then, too, it is possible that in the class of patients with which Craig had to deal, presumably men accepted for service in the United States Army because of their freedom from disease, tuberculosis may have been exceptionally rare, and, of course, by the very terms of his classification a case of suspected tuberculosis would be eliminated from this group. In spite of all this, however, it is remarkable that in 100 patients suffering from other diseases, everyone of them should have given a negative complement-fixation test. In view of all the facts, and in spite of some discrepancies, I believe, with both Bronfenbrenner and Craig, that the tuberculosis antigen will not fix the complement in the presence of syphilitic lipoid antibodies unless tubercular antibodies are also actually present. The vital question as to whether the tuberculosis complement-

[10] Parke, Davis & Co.

fixation test can distinguish between clinically active and inactive cases cannot be given a positive answer excepting with the qualifications above indicated. Bronfenbrenner cautiously says that it seems to answer the requirements both of early diagnosis and of differentiation of active tuberculosis from that in which the pathological condition has apparently been arrested. This is safely conservative, but does not cover the "border-line" cases already referred to. Miller says that with his antigen inactive cases, as a rule, are negative. It seems to me that our conclusion at present must be that complement-binding antibodies are or may be present in the blood of both clinically active and inactive cases; that they may be intermittently absent in both groups of cases but more constantly present in active than in inactive cases, and that the fact of their presence as revealed by this test is valuable information which decides nothing but the existence of a focus which is at least pathologically active.

SUMMARY. Specific complement-binding bodies are present in the blood of patients suffering from tuberculosis. They are not constantly present even in clinically active cases and may be present in cases which have no clinical manifestations. Their presence may be reliably demonstrated by the usual technic. A positive result proves the existence of a tubercular focus, which is at least pathologically active. Its clinical importance, and its relationship to any coexisting syndrome, can only be decided by correlating it with all available clinical data, precisely as in the case of a positive Wassermann in an obscure case. A negative fixation test does not absolutely exclude clinically active tuberculosis any more than a single negative Wassermann excludes clinically active syphilis.

With antigens made from tuberculins or bacillary suspensions the results are at present probably as dependable as the subcutaneous tuberculin test. It is equally applicable in all cases at all times, regardless of fever, low resistance, etc. The subcutaneous tuberculin test, aside from being absolutely prohibited by universal consent in a large group of cases, has in it an element of possible danger difficult to estimate because of the possible or even probable remoteness of effect. Cross-fixations with the Wassermann test mean both tubercular and syphilitic foci. The tuberculosis complement-fixing antibodies are not lipotropic in character but are specific.

While some striking discrepancies exist in clinical reports, the main facts are unimpaired and with due regard to its obvious limitations, the tuberculosis complement-fixation test is a valuable addition to our diagnostic methods.

I wish to express my indebtedness to my clinical assistants, Dr. M. F. Porter, Jr., Dr. B. M. Edlavitch, and Dr. G. B. Kramer for their coöperation in this work.

REPORT OF A CASE OF SCLERODERMA OF THE SKIN.

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The average occurrence of the idiopathic, atrophic dermatitides taken from five large skin clinics in this country and abroad is 1 in every 2580 cases. Since it is so rare, but few cases come under the observation of any one man. To know the different manifestations, symptoms, and complications it is necessary to rely on the experience of others. The greater the number of cases considered the truer the deductions will be drawn. So each case reported will add to the general knowledge of this idiopathic condition.

While reviewing the available literature on this subject the cases reported were tabulated in regard to age, sex, parts affected, and sequence of onset, duration, occupation, treatment, results, and complications. Special note was taken to the frequency of other associated diseases, especially syphilis, tuberculosis, diseases of the thyroid, Raynaud's disease, Addison's disease, and others.

Since this condition was first described by Thirial,[1] in 1845, under the name of ichthyosis, and later in 1854 by Addison,[1] "On the Keloid of Alibert," there have been numerous classifications and names applied to the various forms, all being based on the cutaneous manifestations. There are probably four types which are most generally recognized. Morphea is the name applied by Erasmus Wilson when the condition is that of a circumscribed scleroderma. Scleroderma is a name introduced by Kretschmann. It is defined by Osler as "a nutritional disturbance of the skin, patchy or diffuse, leading to induration and atrophy; usually considered to be a trophoneurosis, the characteristic lesions being areas of skin which are waxy and edematous-looking, surrounded by a violaceous areola, and which gradually become brown, tense, hard, and hide-bound, with increase in collagenous material."

If with this condition contractures are present it is called sclerodactylia.

In 1902 Herxheimer and Hartman classified a group of cases, having similar appearances, under the heading of acrodermatitis chronica atrophicans, the characteristics of cases in this class being:

1. Onset is usually on the backs of the hands and feet, slowly advancing toward the knees and elbows.

2. The disease consists of inflammatory and infiltrative formations, which culminate in atrophy. The atrophy is of a peculiar, wrinkled, cigarette-paper type, to which Jadassohn applied the term "anetodermie."

3. In the edematous stage scleroderma does not show inflammation; this type does.

4. The skin is not hard and adherent, as it is in scleroderma, but is soft and velvety.

5. The presence of an ulnar band, or analogous band of affected skin on legs, and of an immune area, described by Wise, around the genitalia and Scarpa's triangle.

Since 1902 many cases have been reported as belonging to this class. There has been much controversy as to whether these types were different stages in the same process, whether they were different manifestations having the same etiology, or whether they were separate conditions and had different causes. Herxheimer and Hartman, Wise and Snyder and others believe that in acrodermatitis chronica atrophicans the symptom-complex is peculiar to itself and that the constant clinical characteristics, especially the transition from infiltration to atrophy, fully justify its separation from the other forms of diffuse, progressive, cutaneous atrophies.

In tabulating the cases reported an attempt was made to classify the cases under the four divisions above mentioned. This was soon found to be impossible for three reasons: (1) many of the cases presented characteristics of two or more classes; (2) some progressed from one type into that of another; (3) most of the cases were described with such brevity that no classification could be attempted.

The same difficulty was experienced in attempting to classify the case here reported. When first seen the predominating characteristics were those of a disseminated, symmetrical scleroderma. There were areas of waxy or ivory-like spots, surrounded by a violaceous areola. There were areas of atrophic skin that were stiff and adherent, and which could not be picked up between the fingers. The immune area of Scarpa's triangle, described by Wise and Snyder as one of the characteristics of acrodermatitis chronica atrophicans, showed the most marked involvement. The skin over the left ulnar region was of the waxy-edematous type. Over the knees there were patches of the waxy type surrounded by firm, violaceous skin. While under observation the skin in her left forearm changed from the white, edematous type to the pink, atrophic stage, showing the typical ulnar band. The other white areas decreased in size. The hard, adherent, atrophic skin over the hips and sides became softer, more wrinkled, and could be rolled between the fingers—the typical anetodermie of Jadassohn. Histological examination showed less cellular infiltration and more atrophy, so at present this case would be classified probably as a typical case of acrodermatitis chronica atrophicans.

Case Report. The patient is a German woman, age fifty-seven years. She entered Lakeside Hospital June 1, 1915, complaining

of stiffness of the skin, associated with a pricking pain in the affected areas:

Family History. Her father died as result of an accident. Her mother died from apoplexy, at the age of seventy-four years. She had three brothers, two died in infancy and the other one from typhoid fever. One sister is living, but probably has tuberculosis. There is no family history of cardiac or renal disease, rheumatism, insanity, or syphilis.

Personal History. She had chicken-pox and measles when a child. During the past twenty years she has had occasional attacks of articular rheumatism.

Head. She has had severe, throbbing, occipital headaches for a number of years. They are worse at night. In the last four years she has had frequent dizzy spells, often followed by fainting.

Eyes. In June, 1914, while sitting sewing she had a peculiar sensation in her head, and then became unconscious. She regained consciousness the next day. Following this she felt very weak and there was a ptosis of her right eye, which gradually cleared up. Since then she has had some diplopia with increased lachrymation. The throbbing headaches have been more frequent and she often experiences a sound which she describes as of escaping steam.

Ears. Four years ago she had a bilateral suppurative otitis media. This was more severe on her right side.

Nose. Until the age of eighteen years she had very frequent and severe attacks of tonsillitis. Her gums bleed easily. She wears an upper plate; there are frequent sores on the mucous membranes.

Neck. At the age of eleven years a very large abscess developed on the left submaxillary region. In about five weeks this opened spontaneously with a very profuse discharge. The sinus was slow in healing.

Cardiorespiratory. When ten years old she became frightened and ran a great distance. The next day her hands and feet became swollen. She was confined to bed for several weeks. Since then she has palpitation and dyspnea on exertion. She is subject to colds and has a chronic morning cough. She has frequent attacks of pleurisy and occasionally night-sweats.

Gastro-intestinal. About eighteen years ago she had two attacks of peritonitis and four years ago was jaundiced. Her appetite has been good but her digestion has been poor, having flatulence after meals, especially if she eats meat. She vomits frequently and is constipated. She has had two operations for hemorrhoids. With the one a year ago a mass was removed from her rectum, and there was a partial stenosis resulting from the first operation.

Genito-urinary. She has had pyuria, dysuria, incontinence, and frequency of urination for years. She denies ever having had a venereal disease, but thinks her husband did.

Menstrual. Menses began at the age of sixteen years, was always irregular, small in amount and painful, and of about three days' duration.

Marital. Married at the age of seventeen years. She has had nine pregnancies, all the labors being difficult. There were two miscarriages. One child died of diphtheria and measles and one of

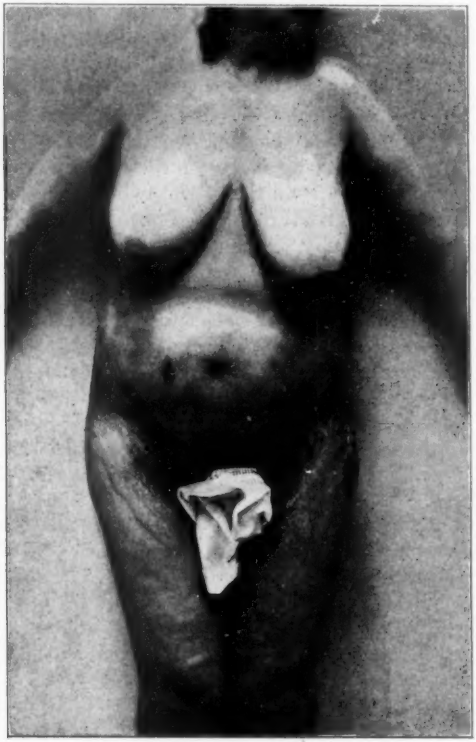


FIG. 1.—Showing involvement of the skin of arms, abdomen and legs. The "immune area" below Poupart's ligament is affected the most. The scar shows where a section was removed.

pneumonia. She now has five children, living and in good health. Her husband is dying from carcinoma of the liver.

Habits. Previous to four years ago she always slept well, worked hard, and had a good appetitite. She drinks one cup of tea or coffee with her meals, and does not use alcohol or drugs. Average weight is 220 pounds.

Nine years ago (1906) she observed a small pin-point elevated

red spot on the skin under her right breast the size of a large bean. It was removed by application of caustics. During its removal her right arm became paralyzed and remained that way for two months.

Present Illness. The patient dates her present illness back five years (1910). At that time she had an abscess in her right hip. This was incised and drained. Immediately following this opera-

FIG. 2.—Showing anetodermia of thigh and location of section removed.

tion her hands and feet became swollen. The right middle, ring, and little fingers were affected first. When the left fingers and hand became swollen. On the dorsum of the second phalanx of the right middle finger there would appear a transitory purple color, and coincident with it a tingling sensation. This discoloration and tingling sensation soon involved the fingers of both hands. She could not bend her fingers, due, she thinks, to the swelling. The

skin affected would not perspire, but her head perspired very freely. Three years ago she took some electric baths. This caused the skin to perspire. The swelling and stiffness diminished. While taking these baths a small white elevated nodule, surrounded by a violaceous color, was observed in the left Scarpa triangle. The discoloration gradually enlarged until it involved both hips and legs above the knees.

February 1, 1913, her rectum was operated on. Following this operation her hands again became swollen and painful. The discoloration present only on the legs and hands was now observed to spread over her abdomen as far as her breasts.

FIG. 3.—Section removed from area shown in Fig. 1, showing marked cellular infiltration of the corium, and a diminished papillary layer.

On the back of her right wrist there appeared at this time a mass about the size of a walnut. It was soft and movable, and the skin was movable over it. She observed crepitation when she moved it. She massaged this mass and in nine months it had disappeared, together with much of the swelling.

June, 1915, a similar mass appeared on the back of the left wrist and still is present.

During the last three years locomotion has been interfered with, due to the stiffness and fixation of the skin over the joints. She has found that cold aggravates the condition and increases the discomfort; also the presence of meat and fish in her diet. For the past eight months she says the skin of her face feels stiff, as though there were a tight band around her forehead.

There have been no areas of gangrene or ulceration. Over the hips, where the skin is very tense, there has been an occasional fissure, which has always healed rapidly.

Physical Examination. The patient is a well-developed, well-nourished German woman, of average intelligence. She lies in bed, active dorsal position, complaining of a burning discoloration of portions of her body.

Head. Is well formed. There is no tenderness or deformities.

Ears. The left aural canal is filled with cerumen. Bone conduction is better than air conduction on that side. The right membrane is thickened. Hearing is diminished on this side and air conduction is better than bone conduction.

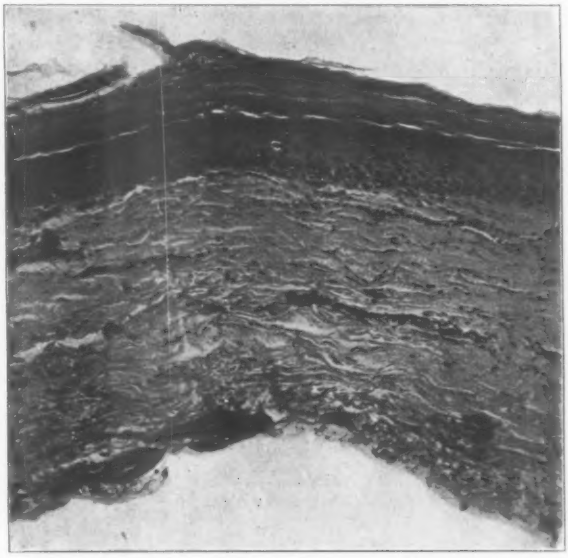


FIG. 4.—Section from area shown in Fig. 2, showing no cellular infiltration, complete absence of papillary pegs, and atrophy of epithelium.

Eyes. There is no ptosis, strabismus, nystagmus, or exophthalmos; the pupils are equal and regular. They react to light and accommodation; extra-ocular movements are good.

Neck. There is a higher pitched note to percussion at both apices, with a few fine, moist rales audible at the right apex. There is a soft, blowing murmur accompanying the diastolic sound and heard best over the aortic area.

Blood-pressure. Systolic, 132. Diastolic, 70. Otherwise the examination of thorax, heart, and abdomen is negative.

Extremities. Flexion and extension is limited in the left knee, due to the stiffness of skin. There are some varicosities. Glands are not abnormally enlarged.

Reflexes. The knee-kick, biceps, triceps, supinator longus and abdominal reflexes are active and equal. The Achilles could not be elicited.

Neuromuscular. There is no acro-ataxia. The proximal ataxia is doubtful. She has a positive Rhomberg's. No Babinski, Gordon, or Oppenheim. Sensation of touch and vibration is perceived

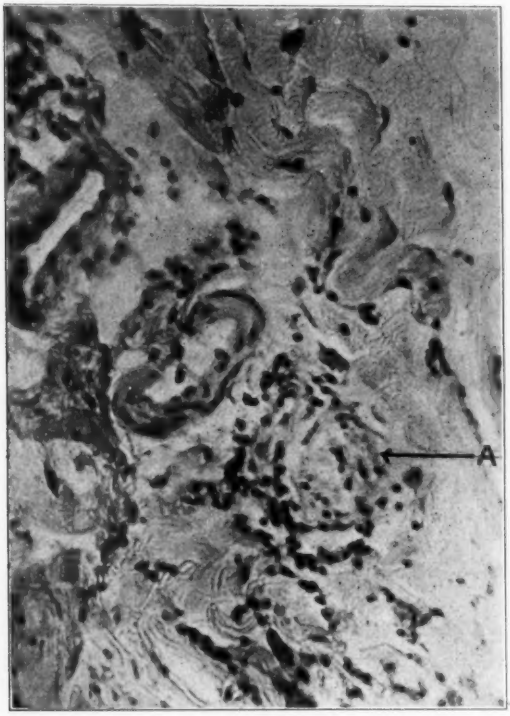


FIG. 5.—Section through a vein, artery, and nerve, which shows cellular infiltration and edema of the nerve (*A*).

throughout. Pain is perceived, but there is an apparent delay of three seconds in transmission. Temperature is less acutely perceived over the affected areas.

Cranial Nerves. There is no disturbance of the cranial nerves with the possible exception of the seventh. The labionasal sulcus is deeper on the left isde; the left angle of the mouth is raised

higher when she smiles. There is the subjective sign of diplopia, but no objective signs of any disturbance in the extra-ocular movements.

Skin. There are three stages represented on the skin. (1) Areas of white, opaque, or waxy, swollen appearance. There are two such areas, about the size of a dollar, one on each side of the umbilicus, and one about twice that size over each gluteal muscle. One above the left patella and on the ulnar aspect of the left arm. (2) Surrounding these areas the skin is smooth, edematous-looking,

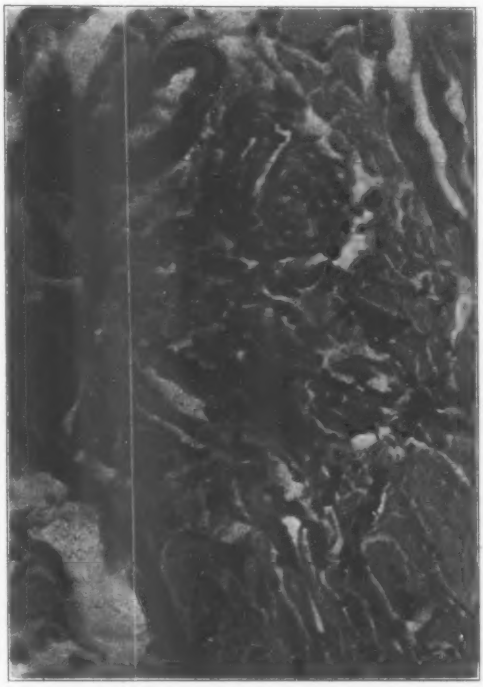


FIG. 6

and of a translucent, violaceous tinge. In places the veins are very easily seen through this. From the breasts down to a point midway between the knee and thigh there is a gradual transition from the smooth, violaceous appearance to the third stage. (3) Here the skin is brown, wrinkled, resembling crumpled cigarette paper, quite thin, and over the hips adherent. In places it is scaly. There are patches of this type of skin on the dorsum of her left ankle, both sides of her knees, both axillæ, and extensor surfaces of both elbows.

Over the joints the skin is not as wrinkled, but it is hard and tense, and cannot be picked up between the fingers.

There is a small, pea-sized nodule in the left Scarpa triangle. It is brown and slightly elevated, and is in the integument.

Laboratory Examination. Hemoglobin, 80 per cent.; red blood count, 4,840,000; white blood count, 6600; differential count of 300 cells: large mononuclear, 8 per cent.; small mononuclear, 18 per cent.; transitionals, 4 per cent.; polymorphonuclears, 68 per cent.; eosinophiles, 2.2 per cent.; basophiles, none. No abnormal red blood cells were seen.

Spinal fluid was clear, but under increased pressure. Pipette count 5 per c.mm. Sicard: 3 cells per high, dry field (all mononuclear lymphocytes). Noguchi's and Fehling's tests were negative. Wassermann reaction negative on blood and spinal fluid. Urine analysis negative.

Subsequent Course. Patient has a constant elevation of temperature of 100°. She could not remain in the hospital on account of sickness of her husband, but promised to return when unencumbered by him. Thyroid treatment discontinued after four days, and she received no therapy until the second admission, Octover 19, 1915, her husband in the meantime having died.

October 19, 1915: Patient again entered the hospital for further observation. At this time she complained of throbbing pains over the abdomen, left leg, and arm. There has been no change in the physical findings, except in the skin.

At this time the skin of the face is not visibly affected. Over the thorax the condition is the same, except that the discoloration has extended on the right up over the clavicle. The two waxy areas below the umbilicus are smaller. On the back, in the rhomboid space, there is a faint violaceous discoloration that was not present before. The waxy area on the left ulnar area has now become of a pinkish hue, and is less edematous in appearance, more translucent, and the veins easily seen.

The violet patches around the knees and ankles are larger. The skin over the abdomen and hips is softer, more pliable, and less scaly. The lump on the dorsum of the left hand is unchanged.

Sensations of touch, pain, and temperature are present and equal throughout; sensation of vibration is diminished over the affected areas.

Blood Examination. Hemoglobin, 80 per cent.; red blood count, 4,440,000; white blood count, 6400; differential count of 200 cells: Large mononuclears, 5.5 per cent.; small mononuclears, 16 per cent.; transitionals, 4.5 per cent.; polymorphonuclears, 74 per cent.; eosinophiles, 2.5 per cent.; basophiles, 1.5 per cent.

Gastric and Duodenal Examination. A duodenal tube was passed on a fifteen-hour fasting stomach. Gastric secretions were clear and opalescent, with a small amount of mucus: Free HCl, 0. Total

acidity, 20. No blood or bile. Duodenal secretion obtained in thirty minutes, a clear amber. No mucus; no blood; free HCl, 0. Total acidity, 14. Lactic, 0. Microscopic examination showed no pus, abnormal detritus, or cellular elements.

Patient was now having an evening elevation of temperature to 101°, with no physical findings to account for it.

She was put on a constant diet of protein, 75 gms.; carbohydrates, 200 gms.; fats q. s. to make 1600 calories. Her total nitrogen, blood-sugar, and sugar tolerance while on this diet was estimated. She was then given thyroid extract, gr. 5, t. i. d., p. c., and again estimated her blood-sugar, sugar tolerance, and total nitrogen. The results are charted below. The sugar-tolerance test was not satisfactory, for the patient vomited a small amount of glucose; the second time there was such a small amount of sugar in the urine that a quantitative test could not be made. However, by using Folin's method of extracting the creatinin and centrifuging the reduced copper was obtained and the amount estimated by Bertrand's method. The amount was too small to be read on Bertrand's table in terms of sugar, so the results only show the amount of copper reduced and not the amount of sugar.

Patient was discharged November 10, 1915, with instructions to continue the thyroid and dilute hydrochloric acid. She was seen at intervals in the dispensary by Dr. Cole. She developed marked palpitation and was very nervous, so the thyroid was discontinued.

January, 1916, she began to have a sanguineous discharge from her vagina, and again entered the hospital on the gynecological service. A dilatation and curettage was done and the curettings were found to be normal. While under the anesthetic two more sections of skin were removed.

On her last admission, January 20, 1916, the skin was much softer. The violaceous band extending over her right clavicle had disappeared. The areas around the knees and ankles were smaller and softer. The lump on the dorsum of her left hand had entirely disappeared. Subjectively she was more comfortable. There was no tingling sensation in the skin, and she complained less of stiffness. There is now a definite violaceous ulnar band on her left arm. The points of interest in this case are:

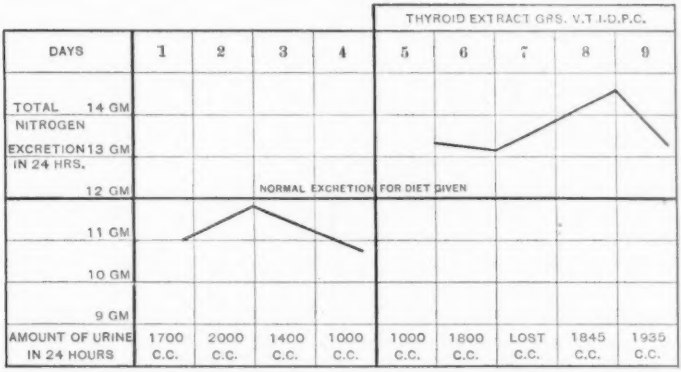
The mode of onset on the distal parts, following infection and operations.

The formation of subcutaneous nodules, described in other cases reported by Stebbing, Kingsbury and Bromwell.

The presence of an ulnar band, which Herxheimer, Hartman and Wise lay stress on in the so-called cases of acrodermatitis chronica atrophicans.

The most marked involvement of Scarpa's triangle, which is described by Herxheimer, Hartman and Wise as usually unaffected.

The improvement observed with thyroid extract and with care in improving the gastro-intestinal function.



Pathological Examination. Two sections of skin were removed in June, 1915, a local anesthetic of novocain being used. The tissue was fixed in 4 per cent. formalin. One section was taken from the edge of the white waxy area on the right side of her abdomen. This section also included a piece of the surrounding violaceous area. Another section was removed from her left buttock, where the skin was thin, hard, wrinkled, adherent, and of a brownish hue.

In January, 1916, while the patient was under a nitrous oxide anesthetic, a piece was removed from her side where the skin was extremely thin, non-adherent, and having the typical appearance of wrinkled brown cigarette-paper. Specimens were fixed in alcohol, Zenker's, and 4 per cent. formalin. Stains were made with hematoxylin and eosin, Weigert's, Van Geison's, Unna's orcein, methylene blue, and eosin.

From the examination of the different sections obtained it was apparent that each section showed one stage of a general process, and that this process was of two general types, beginning with inflammation and terminating in atrophy. The earliest changes noted were found in sections of the waxy area on the abdomen: These sections showed no parakeratosis. The stratum lucidum was fairly well defined. The stratum granulosum was present, but not well defined. The stratum spinulosum was reduced in thickness and intercellular bridges were short. The basal cells took a weak stain and showed some vacuolization. Papillæ were present but were small.

Pars Reticularis. In the upper portion of the pars reticularis, immediately beneath the pars papillaris, the collagenous material

stained weakly and was more homogeneous than lower down. It showed fine fibrillary structure. There were occasional groups of small lymphocytes with a few plasma cells. The bloodvessels showed no changes in number, size, or thickness, but there was a slight cellular infiltration around them. Elastic fibers were present.

The middle and lower portions of the pars reticularis showed bundles of collagenous material, staining well, and in places separated by groups of lymphocytes. The lymph spaces were large. Elastic tissue was present. The bloodvessels here showed some endothelial proliferation. There was a marked infiltration around the bloodvessels and sweat glands. Subcutaneous fat was present.

The nerves showed a slight thickening of the sheath, with a cellular infiltration, not only around the nerves but also in them, mostly lymphocytic in character. There was a marked parenchymatous degeneration, and but few axis-cylinders were visible.

The sections obtained from the skin of the buttock showed a greater inflammatory condition, with more atrophy, than the sections from the waxy area. The cells in the stratum granulosum were flatter. The stratum spinulosum was thinner; papillæ were nearly absent.

In the pars reticularis the collagenous material was more widely separated. The cellular infiltration was very marked. The bloodvessels were thicker and showed more proliferation than in the first stage. Fibroblasts were more numerous in these sections. There was the same infiltration of the nerves.

In the sections removed from the side the skin was very thin and wrinkled, showing the most atrophy. Here the stratum lucidum was not so well defined. The stratum spinulosum was very thin, the intercellular bridges were short, and there was a complete absence of papillæ.

The collagenous bundles in the pars reticularis were thinner and separated more. There was less cellular infiltration in the skin from this area than was found in the other sections. Elastic fibrils were present, but they were thin and few in number. There were few sweat glands, which, however, were atrophic. There was no subcutaneous fat.

The histological findings in the cases reported have been practically the same as was found in this case, with the exception of the involvement of peripheral nerves and the presence of elastic fibers. In most of the cases there has been a diminution of the elastic fibers in the inflammatory stages and a complete absence in the atrophic stage. In this case they were present in all stages, but somewhat diminished in the atrophic stage.

There was only one other case found in the literature reviewed that showed involvement of the peripheral nerves. Lindsey Steven found in a case that the nerve fibers from the cervical and lumbar plexus showed a well-marked parenchymatous degeneration.

Herxheimer and Hartman, Kansky and Sutton, MacKee, Howell and Wise found no changes in the peripheral nerves. Osler in one case found a thickening of the sheath. However, the change was so marked in our case that we believe great stress should be laid on it.

Clinical Considerations. In the cases reviewed the ages varied from nine years to seventy years, the average being thirty-eight. Fifty-one per cent. were in females and forty-nine per cent. in males.

Occurrence	No. of Cases 68	Hands 60	Feet 39	Face 37	Thorax 26	Abdomen 8
Sequence of onset	47	..	..	..	..	..
Appeared first in	..	35	10	0	1	0
Appeared second in	..	6	12	10	2	1
Appeared third in	..	4	2	6	8	1
Appeared fourth in	..	..	..	2	3	1

The hands were affected in 88 per cent. and affected first in 74.4 per cent. of the cases in all four types. In 40 cases where sensation was mentioned there was no disturbance in 26. Perspiration was absent in 3. There was no hypesthesia to touch, and pain in 3 and a hyperesthesia in 1. Temperature sense disturbed in 8. There was only 1 case reported showing blood changes, a case having an eosinophilia of 35.4 per cent., the polymorphonuclear leukocytic count being 45.6 per cent.

Ulcers were present in 12 cases, over 50 per cent. occurring on the distal portions of the extremities.

The thyroid was found unchanged in 12 cases, atrophic in 3, and hypertrophic in 2.

Syphilis was negative in 13 cases and positive in 9, or 43.0 per cent. Reynaud's disease was present in 4 cases, Addison's disease in 1, tuberculosis in 2, and diabetes in 2.

It has quite generally been accepted that scleroderma is a trophoneurosis and due probably to a disturbance of the thyroid function.

Von Leube[27] first pointed out the coexistence of scleroderma with Basedow's disease.

Osler, Grasset,[27] and Dehu,[27] from the changes in the nervous system, the perversion of nutrition, analogous to that of myxedema, together with Jeanselme, Singer, Hektoen, Leredde, Thomas and others, regarded the cause as that of a thyroid deficiency.

In a series of 31 cases collected by Rocques, 22 showed abnormalities. But in our collected cases only 19 per cent. showed changes in the thyroid. Because it was believed that this condition was due to a thyroid deficiency, thyroid extract has been given and now is generally given empirically. In 11 of the cases thyroid extract alone was given. There was improvement in 2 cases, no improvement in 4, and no change noted in 5 cases. Fibrolysin alone was given in 1 case. Thyroid and fibrolysin were given in 1 case, with no change noted. The other cases were treated with a variety

of drugs, and showed some improvement in 24 cases. No improvement in 13 and no change in 5. In order to observe the effect of thyroid extract not only upon the cutaneous manifestations of this disease but also on her metabolism, our patient was put on a constant diet, consisting of carbohydrates 200 gms., protein 75 gms., and fat q. s. to make 1600 calories. While on this diet the total nitrogen excreted in the urine was estimated every day and her blood-sugar and sugar tolerance determined.

After being on this diet for five days she was then given thyroid extract, gr. v, t. i. d., and the same observations were made.

The results show from the increased nitrogen elimination that the metabolism of protein was increased in her case, and may explain her temporary improvement as well as that of other patients on whom this drug has been exhibited.

The majority of cases followed after exposure, pyogenic infections, or were associated with a chronic debilitating disease. In general, after conditions which lower the vitality of the organism and interfere with metabolism.

The thyroid is not the only gland of internal secretion that is affected. Roux[37] found sclerotic changes in the hypophysis, and believed it to be a functional disturbance of that gland. Changes in the adrenals have been described. Dupre, Kahn, Rosch and others believed in a pluriglandular pathogenesis. Falta and Cassiver believe that in scleroderma the glands of internal secretion are affected, but the process is not primary in the ductless glandular system. Since all the glands of internal secretion may be affected in those having scleroderma, and since they are all probably influenced by the vegetative nervous system, it is possible that a disturbance of this nervous system may be the primary cause, though this has certainly not been proven.

Further evidence of a disturbance in the vegetative system is shown by the disturbance of the sweat glands, the trophic conditions, and vasomotor phenomena, as rush of blood to the head, transient areas of hyperemia, tachycardia, etc.

The following pathological findings show disease of this nervous system. Collier and Wilson[40] found that the cells of the intermedialateral tract were undergoing degeneration. The sympathetic fibers arise from these cells. Knapp[40] reported lesions found in the anterior horn of the cord. Brissaud[40] found changes in the cord about the ependyma.

Howell says the distribution of the lesions tends to be segmental. Hutchinson reports a case in which the distribution of the affected areas corresponds in distribution to that of the sympathetic from the fourth or fifth lumbar segment. Similar conditions are reported by Pringle and by Langley. Lichtwitz has observed degeneration of the chromaffin sympathetic ganglia in a case of scleroderma associated with Addison's disease.

We would also call attention to the changes found in the peripheral nerves in our case.

SUMMARY. Whether derangement of the nervous system be the etiological agent causing this disease we are, of course, unable to say. But having mentioned the findings of others, we will merely summarize and discuss the clinical data seen in our case.

We have to deal with a case of diffuse symmetrical scleroderma of the skin, the same, according to the patient, having begun on the distal extremities following an injury to the hip. While under observation she developed many of the characteristics of acrodermatitis chronica atrophicans (Herxheimer and Hartman, Wise), namely, the ulnar band. Anetodermie with softening of the skin over areas, which before had been hard and board-like in character. However, the patient has at all times had the most severe involvement of the skin in Scarpa's triangle, a portion of the body supposed to be immune to this disease.

Thus we find her to be a mixture of two types of scleroderma. From a search of the literature the same variability is found in many other cases, and while commending the attempt to classify the sclerodermas of the skin, we yet feel that this must be done along rather loose lines. They are quite apt to run over into each other and cause confusion if too narrow lines be drawn.

In this case there was marked improvement of protein metabolism as well as a clinical change for a time on giving her thyroid extract. We would call attention to the protein metabolism as a possible etiological factor in this disease. Moreover, there appeared to be some degenerative changes in the peripheral nerves of diseased areas.

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THE CURE OF PROLAPSE OF THE UTERUS.

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The diversity of opinions expressed in the writings of the modern authorities in regard to etiology and treatment of prolapse of the uterus led to a search of the older literature to see if a period

could be found in which there was a unanimity of thought on this subject. No such period was found; opinions were as diversified and debate as acrimonious a hundred years ago as they are today. In Dewees's *Diseases of Females*, published in 1837, we find a corroboration of this statement. At that period the profession was at loggerheads as to the value of conservative treatment, as instanced by the use of the pessary, astringent douches, astringent applications to the vagina, and the closure of the vagina by adhesions, from the use of caustics on the one hand and operative procedures on the other. Those who opposed the use of pessaries argued that the patients were not cured, that the conditions were made worse as the constant pressure of the passary caused ulceration and eventually cancer, and what seemed an unanswerable argument, that the pessaries caused so much pain that a woman would rather have her prolapse than a pessary. The operation proposed consisted in a denudation of the vulva with suture of the two sides together, so that the opening into the vagina was practically closed. If the operation proved successful then the patient was cured to the extent that the uterus could no longer project from the vagina. Dewees, an ardent advocate of the conservative treatment, gives in detail the method of treatment and recites the objections made against it. He then states: "So that my readers can form their own and unbiased opinion of the value of these two procedures, I will use Dr. F.'s own words in the description of this method." He then quotes Dr. Frick's description of the operation just outlined, and closes the chapter in this manner: "This horrible, severe, and ill-described operation is seriously proposed by Dr. F. as a substitute for the simple, successful, and easily managed pessary."

Diversity of opinion and acrimony in debate are not the only things common to the modern and older writers. Many of the views heralded as new were known years ago. "The ancients doubted the possibility of the uterus being entirely prolapsed on account of the strong support given by its ligaments. Now we scarcely attribute any retaining or holding power to the uterine ligaments. By experiments on the dead body, Professor Burns found that more resistance was afforded to procidentia by the connection of the uterus and vagina to the neighboring parts than by the agency of the ligaments; for although he cut the ligaments, he could not, without much force, make the uterus protrude. A debility and relaxation of the levator ani and perineal muscles, but particularly an extension and slacking of the pelvic fascia, in its connection with the uterus and vagina, are in a great measure essential to the production of the prolapsus." This might well have been written by the most modern advocate of the newer pelvic anatomy, but unfortunately for their priority in this field it is a quotation from Ashwell's *Diseases of Females*, published in 1845.

It may be of interest to review briefly the literature of this subject, showing the views held at different periods. Time will not permit a complete review, so I have divided the subject into ten-year periods, beginning with 1880. Apparently little progress was made in the treatment of prolapse from 1838 to 1880. Except for operations to repair the lacerated cervix and operations on the anterior wall of the vagina introduced by Marion Sims the treatment was practically the same. In Byford's book, published in 1881, are a number of illustrations of the most marvelous and deadly looking pessaries. He also discusses fully the pessary treatment, and expresses himself as favorable to their use. He also states: "An efficient use of astringents would appear in some cases of extreme prolapsus to be sufficient to effect a cure." In regard to surgery he remarks: "Surgeons have generally in their operation addressed themselves to but one item in the case. One party operates on the perineum, restoring or lengthening it, more or less completely to close up the vaginal orifice, while another party lessens the diameter of the vagina itself and condenses its walls into cicatricial or undistensible tissue." This latter was accomplished by the Sims operation or purse-string sutures without denudation.

T. Gaillard Thomas[1] records his method of treatment in a clinical lecture on a case of prolapse complicated by laceration of the cervix. The cervix was made and repaired, using silver wire. He proceeds: "The second step in the case will be the taking of a 'gore,' so to speak, in the anterior wall of the vagina by the operation known as elytrorrhaphy, and then the final operation will consist in the restoration of the destroyed perineum, after which I think the case can be discharged perfectly cured." He also records a second case[2] treated in the like manner. It is interesting to note that in the fifteen communications found in the *Index* for 1880, two dealt with urinary calculi as a complication of prolapse. The majority of the authors held that lacerations of the perineum was the most important etiological factor. W. V. Jackson,[3] however, makes this observation: "I have never seen a case caused by a ruptured perineum nor have I met with a case cured by sewing up such a laceration."

James P. Boyd[4] discussed the causes and treatment of prolapse. He noted that the condition at times appears in virgins. He gave as causes falls, torn perineum, and weight of uterus. His treatment consisted of pessaries, elytrorrhaphy, and narrowing of the vaginal orifice by extensive denudation and suture.

From the excerpts read it will be seen that the surgeons of 1880

[1] Boston Med. and Surg. Jour., October 27, 1881.
[2] Ibid., November 10, 1881.
[3] Australian Med. Jour., December 15, 1881.
[4] Med. Ann., Albany, July 1, 1881.

and 1881 had little concept of the pathological anatomy of the condition and little understanding of its rational treatment. Thomas was in advance of his confrères as an operating surgeon; he failed, though, to understand the anatomical injuries of lacerated perineum, cystocele, and prolapse. It seems odd that the surgeons of that period did not have a clearer understanding of the anatomical relationship of the bladder to the uterus and vagina. Vesico-vaginal fistulæ were more common then than now, as were also vesical calculi, and operations were frequent for the cure of these two conditions.

Ten years show a marked advance in the treatment of prolapse, and we find the surgeons in 1890 making use of the ligamentary supports of the uterus in attempts to effect a cure.

Smyley[5] said: "There are two types of cases, those due to relaxation of the pelvic peritoneum (meaning ligaments) and those due to relaxed and torn perineums." In the former he advised the use of the pessary and in the latter operation on the perineum. He advised Hegar's operation in old women and Martin's operation in women still in the child-bearing period. He reports a case of failure after a Hegar operation which was cured by an Alexander operation. He spoke of the difficulty of finding the ligaments in the inguinal canal, and reports that he practised on the cadaver before attempting the operation on the patient.

The use of the ligamentary supports was not in general use, however. B. C. Hirst[6] reported a case of complete prolapse in a girl, aged seventeen years. He cured the condition by performing a complete anterior colporrhaphy with sunken catgut sutures and by doing a posterior colporrhaphy somewhat after the method of Emmet.

That there was diversity of opinions at this period is shown in an article by I. B. Will.[7] He spoke of the chaotic condition of the subject, both from the stand-points of cause and cure. He said:

"The theories advanced have been well-nigh innumerable and the treatment advanced ranging all the way from that of a Virginia physician who hung his negro patients head downward and poured the vagina full of a decoction of tan bark up to the most expensive silver and gold-plated utero-abdominal supports of modern times, on the one hand, and the narrowing of the vagina by plastic operations to the shortening of the round ligaments on the other." He also spoke of the diversity of opinion on the part of the faculty of the New York Polyclinic Medical School.

The treatment by pelvic massage, after the method of Thure Brandt, of Stockholm, was also in vogue at this period. The treat-

[5] Tr. Royal Acad. Med. in Ireland, 1889, vol. vii.
[6] Univ. Med. Mag., 1889–1890, p. 257.
[7] West. Med. Reporter, December, 1899.

ment was referred to by Alfred J. Smith.[8] The technic of this treatment consists in:

1. Lifting the uterus.
2. Massage of the uterus and its ligaments.
3. Forced separation and forced closure of the knees.
4. In tapotement of the lumbar and sacral vertebra.

The treatment of Thure Brandt has been recently recommended by Boldt, of New York.

In 1900 we find a still further advance in the treatment of prolapse. Watkins[9] discussed methods of treatment in vogue at this time. He considered them under the following heads:

1. Plastic vaginal operations.
2. Plastic vaginal operations combined with abdominal suspension.
3. Hysterectomy.

He then describes his method of operating, which was essentially a vaginal fixation of the uterus. Watkins has eventually developed this operation into one of the most important contributions on the subject of prolapse.

The first vaginal fixation was done by Schucking[10] in 1888. He performed the operation without freeing the bladder from the uterus. The bladder was frequently injured, and his work received little notice. Sanger,[11] in 1888, also described vaginal fixation of the uterus. The operation was also described by Mackenrodt[12] in 1892; Duhrssen[13] in the same year; and by Kuster[14] in 1894. Vaginal suspension was proposed by Vineberg[15] in 1896 and also by Wertheim[16] in the same year. These prior operations had to do with the correction of retrodisplacement of the uterus, and Watkins was the first to make use of the principle for the cure of prolapse. With the development of the method to the present interposition operation are associated the name of Frend, Duhrssen, Schanta and Wertheim.

Gynecologists were not all in accord with Watkins; in fact, it is only during the past few years that his operation has received the attention it deserves. John B. Deaver[17] said: "Three indications are to be met with, as a rule: the vaginal canal and vulva outlet must be restored to their normal condition, the enlarged or subinvoluted uterus corrected, and the uterine support applied from above." He favored ventral fixation, as sufficient support could not be obtained from the ligaments, and advised against vaginal hysterectomy.

[8] Tr. Royal Acad. Med. in Ireland, 1899, vii, 254.
[9] Am. Gynec. and Obst. Jour., 1899, xvi, 420.
[10] Centralbl. f. Gynäk., 1888, No. 12.
[11] Ibid., No. 2, p. 34.
[12] Berlin, Gynec. Sec., May 27, 1892.
[13] Centralbl. f. Gynäk., 1892.
[14] Deutsch. med. Wchnschr., 1894, No. 19.
[15] Med. News, March 14, 1896, p. 288.
[16] Centralbl. f. Gynäk., March 7, 1896.
[17] Am. Jour. Obst., 1900, xli, 478.

Smith,[18] however, advised vaginal hysterectomy, followed by plastic work for prolapse in elderly women. Werder[19] spoke against hysterectomy. He operated as follows:

1. Currettement of the uterus.
2. Amputation of the cervix.
3. Anterior colporrhaphy.
4. Ventral fixation of the uterus.
5. Colporrhaphy.

E. E. Montgomery[20] in discussing Werder's paper suggested shortening of the uterosacral ligaments.

Noble[21] thought the most important part of the operation for the cure of prolapse was the restoration of the perineum.

Fritsch[22] proposed a unique operation. He anteverted the uterus through an anterior vaginal section, brought the fundus down into the vagina and sutured the body of the uterus both to the anterior and posterior vaginal walls. The uterus became a permanent pessary in the vagina.

Here again in this period we see the diversity of opinion as to methods of cure. Marked advance, however, in certain aspects of the cure were made, the realization of the importance of the cystocele and rational methods for its cure proposed by Watkins[23] and Hadra[24] being probably the most important. The realization of the importance of the pelvic fascia as a support of the uterus and the suggestion of Montgomery for the utilization of the uterosacral ligaments were also noteworthy developments. All the radical operations proposed at this period for the cure of prolapse rendered subsequent pregnancy dangerous and sterilization had to be performed in the child-bearing woman.

The literature on this subject from 1900 to the present time is so voluminous that it is practically impossible to review it. Probably the most important papers are those dealing with the anatomy of the pelvis. Of these may be mentioned the description of the ligamentum transversus coli by Mackenrodt, papers by Jellett,[25] Tweedy,[26] Keyes,[27] Williams,[28] Keyes,[29] and Fitzgibbon.[30] Many communications have been presented dealing with the operative cure of prolapse. Of the most important are the various papers of Goffe, dealing with suspension of the bladder as a cure for cystocele and his operation of vaginal shortening of the round ligaments and also vaginal hysterectomy combined with his operation of

[18] Ann. Gynec. and Pediat., 1900, xiii, 813.
[19] Am. Gynec. and Obst. Jour., 1900, xvi, 13.
[20] Ibid.
[21] Ibid.
[22] Loc. cit.
[23] Centralbl. f. Gynäk., 1900, xxiv, 49.
[24] Am. Jour. Obst., 1889, xxii, 470.
[25] Jour. Obst. and Gynec. Brit. Emp., 1912, xxi. Med. Press and Circ., London, 1914, ii.
[26] Jour. Obst. and Gynec. Brit. Emp., 1912, xxi.
[27] Am. Jour. Obst., September, 1913.
[28] Ibid., April, 1915
[29] Ibid., October, 1915.
[30] Surg., Gynec. and Obst., July, 1916.

bladder suspension for the cure of prolapse. Also important were those of Alexandroff[31] and Tweedy[32] dealing with Mackenrodt's ligament for the cure of prolapse; of Jellet[33] on the shortening of the uterosacral ligaments; the perfection of the interposition operation by Watkins and other authors; ventral fixation by Harris, Murphy, Baldy and Kocher, and the Mayo interposition of the broad ligaments.

In spite of the immense amount of careful work done on the anatomy of the pelvis in relation to uterine prolapse, the casual reader is left in a quandary on account of the many diversified opinions as to the value of the supportive power of the various pelvic tissues. For instance, some authors hold that the pelvic floor is all important, others that it gives absolutely no support; others that the uterosacral ligaments are most important, others that they are of no importance; others that the endopelvic fascia is all important, others that it is of no importance; still others that Mackenrodt's ligament is the true support, others that it plays no part in the support; others that the round ligaments have an important function, others that they are useless, and so on *ad infinitum*. The same is true of operative procedures. There has never been in the entire history of uterine prolapse such a diversity of opinion as to etiology and treatment as at the present time.

Much of the confusion results from the idealistic attempts to reach perfection. Some authors consider uterine prolapse a hernia and then proceed not to apply the principles of repair of hernia in other parts of the body. Others dilate on the anatomy of the pelvis and discuss altered anatomical relations and then attempt to restore normal anatomical conditions. This cannot be done; there never has or probably never will be, unless man is given the power of recreation, an operation that will restore either a lacerated perineum or a displaced uterus by restoration of normal anatomy. The utilization of anatomical supports, yes, but not restoration of normal anatomy. As a matter of fact, many of the operations based on the so-called restoration of the normal anatomy depend for their success by distortion of the normal antomical supports. There is no reason why in some cases even that the adventitious supports should not be used to cure prolapse if success can be obtained. No one hesitates to restore a displaced kidney, stomach, colon, or liver by makeshift supports, and we hear nothing of restoring anatomical supports to these organs. We are satisfied if the means used hold the organs in place and cure the principal symptoms and produce no troublesome new symptoms. Why not apply the same principles to the cure of prolapse of the uterus.

Prolapse of the uterus is an abnormal condition, and in that sense a disease, and must be treated as conservatively or as ruthlessly as

[31] Zentralbl. f. Gynäk., Leipzig., 1903, xxvii, 762.
[32] Loc. cit. [33] Loc. cit.

any other diseased organs as the nature of the individual case demands. As a matter of fact, we now have various ways of treating these cases successfully. No one method can be applied to every case, and while we can understand the enthusiasm of the promoter of an operation, for this method it is folly to attempt it.

In treating prolapse of the uterus we must understand the problems to be met in the individual case. What are the conditions which confront us?

1. In all cases of complete prolapse, there is present cystocele-rectocele and prolapse of the uterus. Usually other complications are present, such as endometritis, laceration of the cervix, hypertrophy of the cervix, enlargement or atrophy of the uterus, ulceration of the cervix, and ulceration of the vaginal mucous membrane.
2. Is the prolapse in a multiparous or nulliparous woman?
3. Is the prolapse in a woman before or after the menopause?
4. What is the operative resistance in the patient?

Let us first discuss conditions two and three.

On general principles no operation should be performed on the nulliparous woman in early life that would interfere with or complicate pregnancy or labor. On the other hand, conditions might be such that no such method would suffice to effect a cure. Under such circumstances we would be justified in performing an operation to effect a cure and sacrificing her child-bearing function. The same question arises in the case of the multiparous woman in the child-bearing period, though the loss of function would likely not entail as great a sacrifice on the part of the woman.

This would rule out interposition operations, hysterectomy, all fixation operations, both vaginal and abdominal, unless artificial sterilization was performed at the same time. When it is decided to maintain child-bearing function a choice can be made from the following procedures: Replacement of the bladder by the Goffe method, restoration of the perineum combined with vaginal operations of the round ligaments by the method of Goffe, Vinberg, Wertheim, etc., or abdominal shortening of the round ligaments by any of the many methods or ventral suspension; or the vaginal or abdominal shortening of the uterosacral ligaments or the operation on the ligaments of Mackenrodt after the technic of Alexandroff and Tweedy. If circumstances are present that these operations would not effect a cure, we can then resort to the interposition operation of Watkins, the Mayo operation, Goffe's operation No. 2, vaginal fixation, or abdominal fixation after the methods of Harris, Murphy or Baldy, etc., combined with the necessary plastic work and artificial sterilization. When sterilization is necessary and the uterus is not removed, both Fallopian tubes should be taken out in their entirety. I cannot see what is to be gained by removing a wedge from the cornua of the uterus, cutting out a portion of the tube and burying the end that is left

between the layers of the broad ligament except to complicate the operation.

Women before the menopause present, in addition to that of child-bearing, the question of drainage of menstrual and other uterine discharges. In the still menstruating woman no operation should be performed that will interfere with the drainage of the uterus. This rules out to a great extent the interposition operation, but leaves available all the other procedures subject to the considerations discussed in relation to child-bearing. In the woman after the menopause, none of these restrictions have to be considered and leaves available the operation best suited to the individual case.

Complications found associated with prolapse: Of these the most important is cystocele. Procedures for the cure of the cystocele are just as important as the cure of the prolapse itself. Simple denudation of the anterior vaginal wall is not sufficient to cure cystocele. The interposition operation of Mayo and Watkins in properly selected cases will almost invariably cure the cystocele, while at the same time curing the prolapse. The Goffe operation of suspension of the bladder at a higher level on the uterus or united broad ligaments, with anterior colporrhaphy should form an integral part of all other operative procedures.

Rectocele. An efficient operation for the restoration of the perineum should be performed. Personally, I favor a flap-splitting operation with suture of the levator ani muscles and fascia in the midline between the vagina and the rectum with elevation of the rectum after the method of Ward. A well-performed Emmet or Hirst operation will be just as efficient.

Lacerations of the Cervix. The cervix if lacerated should be repaired or amputated, depending on local conditions present, if the uterus is not to be removed.

Endometritis is present in nearly all cases except in those occurring in women after the menopause. When present the uterus should be curetted or else swabbed out with full strength tincture of iodine.

Ulcerations of the Cervix and Vagina. Unless amputation of the cervix or hysterectomy is to be performed, ulcers of the cervix should be treated and cured before resorting to any operative procedure for the cure of the prolapse. Ulcers of the cervix in women near and after the menopause may be a serious menace as to cancer, and hysterectomy is advisable in women at these periods when the ulcers fail to heal promptly under appropriate treatment. A recent experience of my assistant, Dr. Morrison, has led me to the belief that all cases of indolent ulcer of the cervix complicating prolapse should be examined microscopically before resorting to any operation which does not remove the uterus. He performed a Mayo operation on a woman in the early forties, an apparently

benign ulcer of the cervix was present. Microscopic examination of the specimen showed cancer at the site of ulceration.

When the vagina is ulcerated the ulcers should be cured before operating unless they are so situated that the vaginal denudation will remove them. Hypertrophy of the cervix should be treated by amputation.

Enlargement of the uterus may influence the type of operation to be selected. If enlargement of the uterus be present it should be treated either by complete vaginal hysterectomy, supravaginal hysterectomy by the vaginal or abdominal routes, or by removing a wedge-shape piece from the body of the uterus. When enlargement of the uterus complicates the prolapse the following operations are available: Vaginal hysterectomy followed by the technic of Goffe or Mayo; Watkins interposition operation with reduction of size of the uterus by removing a wedge-shaped piece of the body; supravaginal hysterectomy followed by the Baldy technic of ventral fixation of the cervical stump; Murphy's method of ventral fixation after removing a wedge from the body of the uterus.

Atrophy of Uterus. When the uterus is atrophic, none of the operations upon the various ligaments are likely to prove successful. The Watkins interposition operation is also contra-indicated when the uterus is small. Fixation of the uterus also frequently fails under these circumstances. The best results are probably obtained by the Mayo or Goffe operation. Conditions are such, however, at times that nothing short of obliteration of the vagina will affect a cure.

What is the operative resistance of the patient? The choice of operative procedure will depend upon the condition of the patient. In general, patients with prolapse have lowered tissue tone and are not particularly good surgical risks. On account of the extensive plastic work necessary, operations for the cure of prolapse take a considerable time to perform. Many of the patients are advanced in years and the use of ether and chloroform entail serious dangers to the operations. In the majority of our cases we operate under scopolamin-morphin narcosis alone or with a minimum amount of ether or chloroform, or else under spinal anesthesia.

Vaginal operations, as a rule, are safer than abdominal ones. Some cases, however, are such poor surgical risks that the vaginal operations necessary to effect a cure are contra-indicated on account of the length of time it takes to perform them. In these cases we have resorted to simply doing a high fixation of the uterus under local anesthesia. Of course the cystocele and rectocele are not entirely cured, but the patients are made much more comfortable, inasmuch as a large mass no longer projects from the vagina.

Finally, in those cases which for any reason cannot be operated on we have a very efficient method of treatment in the use of the Menge pessary.

GASTRIC POLYPOSIS.[1]

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Gastric polyposis is a sufficiently rare disease to be of considerable interest. During the past year 2 cases of this affection and an unusual specimen have come under our observation which we wish to report briefly.

Case I.—G.C.D., male, aged fifty-five years, admitted to the Union Protestant Infirmary November 1, 1915, complaining of weakness, anemia, and loss of flesh. Three months before admission the patient was suddenly taken with a severe chill followed by fever. A blood examination revealed malarial parasites, for which quinin was administered. The patient had lost twelve pounds in weight during the last three months. He had no pain, no digestive disturbance, but occasionally felt some discomfort in the lower abdomen. The bowels were regular but the stools were continuously tar-colored.

Physical examination revealed a well-developed, well-nourished man. The skin and mucous membranes are decidedly pale. There is no jaundice. The lungs and heart are normal. The abdomen is soft; there is no tenderness anywhere; no rigidity; no masses; no free fluid in the abdomen. The edge of the liver is palpable; there are no enlarged glands. The contents of the stomach obtained after a test meal contained considerable mucus, and there was an entire absence of free HCl, with a total acidity of 4, and an absence of lactic acid. A retention meal failed to reveal any evidence of the rice taken the evening before. The stools are dark in color and contain large quantities of occult blood. The blood examination reveals a marked secondary anemia, presenting 2,200,000 red cells; the hemoglobin varies between 37 and 55 per cent.

The roentgen-ray examination with a bismuth meal presents a cow-horn stomach of normal size with a very large, persistent filling defect at the junction of the greater curvature and pylorus; there is no obstruction.

On account of the constant bleeding, which was at all times revealed in the stools, the absence of free HCl in the gastric contents, together with a very large and constant filling defect as revealed by the roentgen-ray, the diagnosis of carcinoma of the stomach was

[1] Presented at the meeting of the Association of American Physicians, Atlantic City, May 2, 1917.

made, notwithstanding the fact that the patient had lost but little flesh and had no pain or gastric disturbance.

Operation was advised and was performed November 18, 1915. Upon opening the abdomen a soft tumor, the size of a hen's egg, was palpated on the greater curvature of the stomach near the pylorus. An incision was made on the anterior wall of the stomach and a papillomatous mass with a broad base was observed springing from the posterior wall near the greater curvature. The surface was rough, ulcerated, and hemorrhagic, with numerous papillæ; it was about 7 cm. long, 4 cm. wide, and 5 cm. high. No other tumors were observed in the stomach. The tumor was excised with the electric cautery by making an oval incision around the base, including a good margin of normal tissue.

The patient made a rather uneventful recovery from the operation, but the stools continued to present occult blood. The hemoglobin was constantly low.

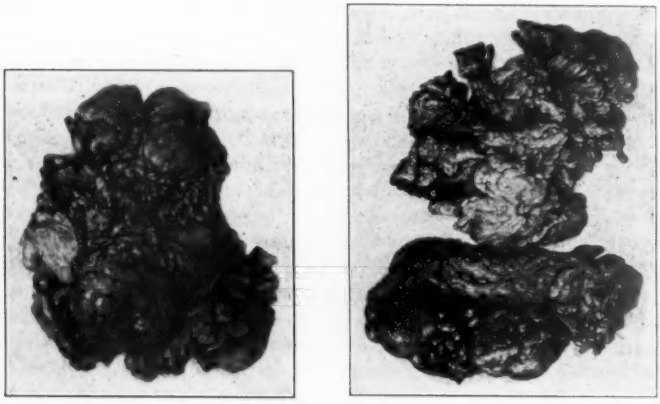

FIG. 1.—Case I.

The pathological report of the growth indicated that it was an adenopapilloma. Cancerous changes were revealed in the base of the growth.

Inasmuch as the patient's general condition did not improve and his anemia continued to increase, as well as on account of the constant appearance of blood in the stools even after numerous transfusions, further exploration was decided upon.

The operation was performed April 6, 1916. The stomach was found in good condition. The duodenum was found adherent to a mass posteriorly, which had apparently eroded into the duodenum. The mass was about the size of a hen's egg and densely

adherent to the abdominal aorta and vena cava. Numerous palpable glands were felt throughout this region. The mass was definitely malignant and its removal impossible. The patient recovered from the operation, but the anemia became more progressive and the stools continued to reveal blood.

Notwithstanding numerous treatments with radium the patient continued to loose flesh and strength, and died of exhaustion October 2, 1916.

CASE II.—G. T. T., aged fifty years, was admitted to the Union Protestant Infirmary March 23, 1916, with a history of indigestion, with which he was first affected nine months ago. There was present pain, fulness, nausea, and vomiting. He had lost twenty-five pounds in weight. There was no history of hematemesis or melena.

On examination the patient is found poorly developed and undernourished. The liver is somewhat enlarged. In the epigastrium there is a sausage-shaped mass moving with the respiration and not tender to pressure. A radiographic examination reveals a large filling defect of a crater-like appearance at the pylorus, indicating an annular carcinoma of the pyloric ring; there is also marked retention (twelve hours). The gastric contents is brownish in character, containing mucus and blood presenting an absence of free HCl, but with a marked lactic acid reaction. The retention meal is positive; the stools contain blood.

A diagnosis of pyloric carcinoma with stenosis was made and operation advised. This was performed by Dr. Chaffee, resident surgeon of the Union Protestant Infirmary, March 26, 1916. On opening the abdomen a large mass presented itself at the pylorus. The tissue was hard and did not give the impression of being carcinomatous, but one enlarged gland was observed. A resection of the stomach containing the mass was made and a posterior gastroenterostomy performed. The patient made a satisfactory recovery.

On incising the resected mass a papilloma revealed itself just within the pylorus, projecting into the lumen so as to nearly occlude the orifice. The base of the growth is hard, indurated, and 3 cm. in diameter; that portion of the papilloma projecting into the pylorus is much softer and is 3 cm. in length. The sections made from the polyp present the typical appearances of malignancy. The carcinoma is of the medullary type in the papilloma and the scirrhus type in the stomach wall.

Of interest in this connection is a specimen found in the museum of the College of Physicians and Surgeons of Baltimore, presenting a typical example of multiple papilloma involving almost the entire stomach. It is interesting to note that that portion involving the pylorus has undergone a malignant degeneration.

A most exhaustive study of gastric adenopapillomata was published by Epstein in 1864, in which he collected 14 cases in 600

autopsies; he also collected 8 other cases from literature. Of these 22 cases 12 are solitary and the other 10 consisted of 9 small and 1 large polyp.

As regards etiology, most authorities point to a chronic gastritis as an underlying factor in the production of gastric adenopapillomata. The disease is more apt to occur in males than females, and in most instances after the fortieth year of life.

FIG. 2.—Case II.

There are great variations as to the number of polypi that may be present, varying in individual cases from 100 to 200. They may also vary as to size from that of a pea to a hazel-nut, and may be as much as 2 or 3 cm. in length. They usually present a reddish or grayish aspect and are rather soft in consistency.

They are frequently pedunculated or attached by broad bases, or often club-shaped or cylindrical and frequently pigmented, the color depending upon the degree of vascularity. These growths may take their origin from any part of the gastric mucous membrane, the membrane covering them being smooth or villous.

The usual location of the growths is at the pylorus, although any portion of the stomach may be involved.

According to Menetrier there are two distinct types of gastric polyps depending upon whether the hypertrophy and hyperplasia involve the excretory or the deeper portions of the tubular glands. In the first type lobulation is more apparent and cystic forms are more common, the orifices of the excretory ducts being obliterated by the growth of the interglandular connective tissue. In the second type, those in which the deeper portions of the glands are

FIG. 3.—Case II. Specimen in museum of College of Physicians and Surgeons, Baltimore.

involved, the polyps are uniform and tubulation is less pronounced. Between the two forms of polyadenomata there are a number of intermediate types; these mixed types are most common.

The mucous membrane not involved in the disease may present the appearance of a chronic gastritis. It may be congested, presenting hemorrhagic erosions with pigmentation. The polyadenoma "en nappe" of Menetrier is much less common. In this variety the hypertrophy and hyperplasia involve the entire mucous membrane in a certain area, thus developing into large plaques, and not as simple polypoid vegetations.

Microscopically polyps consist, according to Meyer, of hypertrophied mucous membrane muscularis mucosa and a connective-tissue core containing fairly large bloodvessels. The polyp presents on section three lobules, each of which contains a part of the core, here consisting of connective tissue and muscularis mucosa. The hypertrophied mucous membrane contains enlarged glands with dilated lumens. The glands are surrounded with columnar cells with basal nuclei; a large number of goblet cells are present, secreting mucus into the lumen of the gland. The interstitial tissue between the glands contains lymphoid cells, plasma cells, eosinophiles, and polynuclear leukocytes.

Inasmuch as polypi of the stomach are usually benign in character they may be present for a long period of time without producing symptoms. In fact, this affection is most frequently so obscure that a correct diagnosis is only revealed at operation or at autopsy. In some instances the symptoms are extremely severe; there may be present intense anorexia, edema, and ascites, producing a symptom-complex much like that of cirrhosis of the liver. Occasionally a diagnosis is made possible by the finding of a fragment of a polyp in the wash-water during lavage, such as was observed in Meyer's case, and at times by the presence of a large polyp in the stools. In the extensive forms of gastric polyadenoma, roentgen-ray examination is often very conclusive. There is, according to Meyer, a "mottled appearance of the entire right half of the stomach as if the bismuth were trickling through and around numerous masses together with the irregular and indefinite outline of the stomach." The condition may be mistaken for an achylia gastrica, inasmuch as polyps of the stomach are usually associated with absence of gastric secretion; the great excess of mucus, however, together with the unusual character of the mucus, of the peculiar egg-white appearance, distinguish this condition from an achylia gastrica. A most important and constant finding, too, is the presence of fresh blood appearing constantly in the gastric contents, especially, as Meyer points out, when observed in cases of achylia gastrica with normal or increased gastric motility, inasmuch as in those cases of hemorrhage due to ulcer there is usually hyperacidity with diminished motility.

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ETIOLOGY AND TREATMENT OF HEMORRHAGIC DISEASES.

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The group of hemorrhagic diseases is a heterogeneous one comprising a number of conditions of very diverse pathogenesis. For practical purposes it has been the custom of clinicians to include in this group not only those diseases, such as hemophilia and the purpuras, in which a tendency to uncontrollable hemorrhage is the essential clinical manifestation of the disease, but also many dissimilar conditions in which a hemorrhagic tendency may be observed at some stage in the course of the disease. To this secondary group belong aplastic anemias, the leukemias, hepatic disease, and some of the infections and intoxications.

During the past few years the pathogenesis of the hemorrhages in this diverse disease group has been the subject of active study both in laboratory and clinic. This work has pointed the way toward a more logical classification of the various types of hemorrhagic disease, and much of value has been learned concerning their points of difference. The great advances which have been made in this direction are due in great measure to a change in our view-point regarding the relative importance of structural and of physiological pathology in the search for the causes of disease; and I believe that we owe in large part the additions which have been made in the past decade to our knowledge of the pathogenesis of the hemorrhagic group of diseases to an abandonment of the search for abnormal structure and to the vigorous application of biochemical and biophysical methods to the problem of blood coagulation in health and in disease.

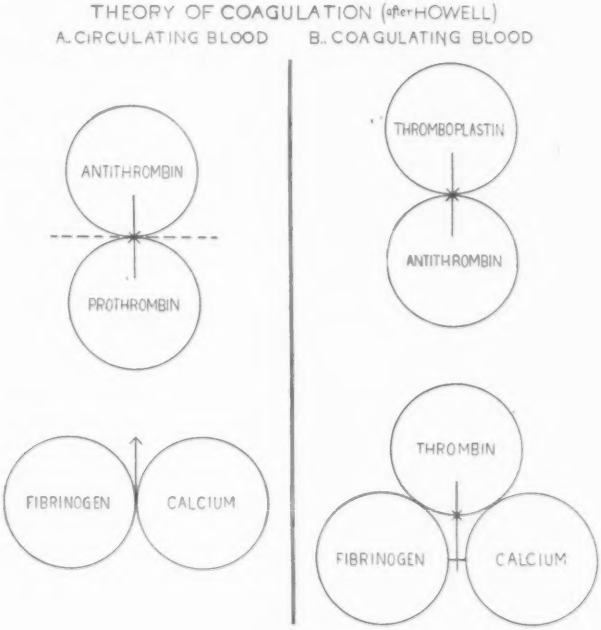
Although it may be premature to speak of an etiological classification of hemorrhagic diseases, it cannot fail to be helpful to student, physician, and original investigator alike to take stock of what has been accomplished toward such a classification and to indicate how the results of these studies may be of help in diagnosis and in the formulation of a more rational and a more critical therapy.

Those who may be familiar with the literature on blood coagulation will know perhaps that not all of the elements concerned in clotting of normal blood are clearly understood. In fact, the theories of blood coagulation advanced by various workers differ widely both as to the number of factors which enter into the process as well as in the manner in which they act. It must be clear therefore that this uncertainty concerning the normal process of blood coagulation would lead to many divergent views regarding the forces at work in the coagulation of abnormal or pathological blood.

The theories given to explain the clotting of normal blood are many and intricate. One could hardly attempt to present them adequately within narrow compass. It is, however, essential to a clear understanding of the deviations from the normal which may occur in disease to have clearly in mind a few facts which have some basis in experiment. The theory of Howell satisfies the known facts of coagulation better than any other view thus far advanced, and we may accept his theory as a working hypothesis until further experiment has shown it to be untenable.

According to Howell there are five factors concerned in the clotting of normal blood—prothrombin, antithrombin, thromboplastin, fibrinogen, and calcium. All of these elements except thromboplastin are present in circulating blood. Within the blood-vessels prothrombin is held in combination with antithrombin and intravascular clotting is thereby prevented. When, however, blood is shed the antithrombin is neutralized by the thromboplastic substance of the tissue juices (blood cells, endothelial cells, platelets,

etc.). The liberated prothrombin is now activated by the calcium, and the thrombin which results converts soluble fibrinogen into the insoluble fibrin or the clot.



For purposes of clearness I have given a diagrammatic presentation of the conditions as we now know them to exist in the circulating blood and in the blood when it clots. It must be kept in mind, however, that such diagrams help only to visualize the process. They do not, of course, tell us the true nature of the phenomena concerned any more than graphic presentations of Ehrlich's side-chain theory tell us about the fundamental basis of infection and immunity.

This view of Howell has been the outcome of experiment and of the development of new methods of study. It is full of promise of applications in clinical work, both diagnostic and therapeutic. Already the use of his methods has made possible the classification of some of the conditions of this heterogeneous group on the basis of a defect in one or another element concerned in the clotting of normal blood. But before proceeding to a discussion of the results of such studies, it may be well to outline briefly the useful clinical methods which are now available for studying the pathogenesis

of the various types of hemorrhagic disease. These methods should be employed by anyone who would gain a better knowledge of the defect present in the condition studied or who would desire to have a better basis for instituting rational therapy. These methods are now sufficiently simple to be of value in the hands of clinicians not possessed of extensive laboratory equipment, and surely all practical workers in hematology cannot afford to be without a knowledge of them.

METHODS OF STUDY. 1. *Determination of the Coagulation Time.* It is not necessary to review at this time the numerous methods which have been recommended for the determination of the coagulation time. I wish simply to call attention to several requirements which must be complied with if the results obtained are to be reliable. In the first place all specimens of blood obtained for a determination of coagulation time should be as free as possible from admixture with tissue juices, and secondly a comparison should always be made in each instance with a specimen of blood taken from a normal individual with the same precautions. Judged by these criteria the methods of determining blood coagulability by skin puncture are unreliable and should be discarded. Probably the most accurate method thus far available is that recommended by Howell. This worker aspirates blood directly from the median basilic vein into a syringe coated on the inside with a thin layer of a petrolatum-ether mixture. Two c.c. are immediately expelled into a wide tube, about 21 mm. in diameter (the test-tubes ordinarily used in bacteriological laboratories serve well for this purpose), which has been especially cleaned with a bichromate acid mixture. The period elapsing between the moment the blood is drawn and the moment at which an invertible clot has formed is regarded as the coagulation time. By this method the coagulation time of normal blood averages about twenty minutes. Reliable results are obtained only when the needle of the syringe enters the vein readily and when there is a minimal amount of admixture with tissue juice.

2. *Determination of Bleeding Time.* According to Duke the bleeding time is the tendency to bleed from a fresh cut. The duration of such a hemorrhage is determined by blotting upon absorbent paper all the blood which flows from a small incision at intervals of thirty seconds. Each drop will give in a rough way the volume of blood shed in the given time interval, and the total duration of such a hemorrhage will represent the bleeding time. The normal bleeding time varies from one to three minutes. It should be kept in mind that the bleeding time is independent of the coagulation time. A determination of the bleeding time yields information concerning not only the elements as they exist in the circulating blood, but also additional knowledge of value as regards the potency of the tissue juices, the mechanical and chemical action of the blood platelets, and the elasticity of the skin. Subsequently, in connection with a

discussion of the individual disease types, it will be pointed out that the bleeding time may be normal when the coagulation time is delayed, or the reverse. A knowledge of the bleeding time has been shown to be of value not only from a diagnostic view-point, but also from the stand-point of surgical interference. We believe it desirable that such knowledge should be obtained preliminary to any surgical operation on a patient in whom there may be a tendency to immediate hemorrhage from one cause or another.

3. *Retraction of the Clot and Enumeration of Blood Platelets.* Normally, a blood clot quickly retracts from the sides of the vessel in which it is contained and expresses serum. This phenomenon has been ascribed to the presence of the blood platelets, so that it is not surprising that a low platelet count and non-retractility of the clot are so frequently encountered in the same hemorrhagic condition. The presence or absence of clot retention is determined simply by incubating the clot at 37° C. for from twelve to twenty-four hours. For this purpose it is time-saving to use the same specimen employed for the determination of the coagulation time. In normal blood, retraction begins after several hours, and is complete within eighteen to twenty-four hours; in pathological blood, on the contrary, contraction may occur only after a long time or not at all.

For the enumeration of blood platelets a number of methods are available, but that of Wright and Kinnicutt[14] appears to have given the most reliable results in the hands of most workers. The method may be recommended because of its simplicity. It has now come into general use, and detailed descriptions of the technic will be found in recent editions of works on clinical pathology.

4. *Quantitation of Prothrombin and Fibrinogen.* Of the methods at present employed for a determination of the fibrin factors only two have reached the stage of simplicity which makes their use as clinical tests possible. An idea of the relative amount or relative strength of the prothrombin in the blood may be obtained by a simple method devised by Howell.[1] In this paper it will not be possible to enter into an explanation of the principles upon which the test is based. I shall merely outline the reaction as it is carried out in practice: To a series of tubes containing a constant amount of the oxalated plasma (1 part of 1 per cent. solution of sodium oxalate made up in 0.9 per cent. solution of sodium chloride to 9 parts of blood) is added dilute calcium chloride (0.5 per cent.), 1 drop to the first, 2 drops to the second, and so on up to 4 drops to the fourth tube. Coagulation will result and the time of coagulation as measured by the invertibility of the clot will be shortest in the tube containing the optimum amount of calcium. Tested by this method the clotting time of normal human blood averages about ten minutes; whereas the coagulation of pathological blood (hemophilia) may at times be delayed sixty minutes or more. This test, as will be pointed out later, gives a simple and reliable means of

diagnosing hemophilia *in vitro*, and we believe should be part of the routine examination of the blood in a patient presenting hemorrhagic symptoms.

Fibrinogen can be determined accurately only by gravimetric means. But this method is not suitable for clinical purposes. It is possible, however, to get a good idea of the fibrinogen content of the blood by an examination of the blood clots in a small test-tube, or better still, by clotting a little oxalated plasma by means of calcium, from which a rough estimation of the amount of fibrinogen is possible.

An accurate determination of antithrombin requires the preparation and use of pure solutions of thrombin and fibrinogen, a task beyond the scope of the clinical worker. Until some simpler technic can therefore be devised for quantitating this substance it will be necessary for the present to assume that an excess of antithrombin is responsible for a hemorrhagic condition only if the other factors have been shown to be present in normal amounts.

The calcium factor, too, may at the present time be neglected, for there is no evidence that any form of hemorrhage is referable to an abnormality in this element. In icterus, to be sure, bleeding may be attributable to an abnormality in calcium. It has been shown, however, that the blood calcium in this condition is not actually diminished in amount, but rather is bound by bile pigments, and therefore only slowly available for the requirements of coagulation. This functional deficiency of calcium in cholemia is simple to demonstrate by the "calcium *in vitro* test" of Lee and Vincent. This test is done in a simple control determination of the coagulation time by the use of a second determination with 3 drops of calcium chloride (1 per cent. solution) to 1 c.c. of blood or to 2 c.c., if the technic above described is followed. The addition of calcium will accelerate the clotting of blood from cases of obstructive jaundice, but will not influence control determinations similarly made on normal blood.

5. *Fibrinolysis.* Fibrin-dissolving ferments may be responsible for the hemorrhages in some cases. Even when the blood coagulates normally the clots are not permanent, and oozing may continue through the softened and dissolved clots which form at the site of injury. The presence or absence of fibrinolytic ferments can be detected by incubating the clot at body temperature and noting whether any dissolution occurs in a stated time interval. Since the clot from any specimen of blood will undergo a certain amount of dissolution if left in its serum a sufficient length of time, it is well to restrict the term pathological fibrinolysis to instances of complete clot dissolution occurring within twelve hours when the blood is kept at body temperature.

THE DIFFERENTIAL DIAGNOSIS OF HEMORRHAGIC DISEASES BASED UPON A STUDY OF THE BLOOD. In gathering together the results of the numerous studies made upon some of the diseases of

THE DIFFERENTIAL DIAGNOSIS OF HEMORRHAGIC DISEASES BASED UPON A STUDY OF THE BLOOD.

Hemorrhagic diseases.	Coagulation time.	Bleeding time.	Number of platelets.	Retractility of clot.	Factors of coagulation.				Fibrinolysis.	Remarks.
					Prothrombin.	Antithrombin.	Fibrinogen.	Calcium.		
I. Primary hemorrhagic disease.										
A. Hemophilia[1 2 3*]	Prolonged	Normal	Normal	Normal	Diminished	Relatively increased	Normal	Normal[3]	Negative	Demonstration of prothrombin deficiency is a reliable *in vitro* test for the diagnosis of the hemophilic condition.
B. Morbus maculosus neonatorum[5 6]	Prolonged	Normal	..	Normal	Diminished	Normal	Normal	Normal		
C. Purpura hemorrhagica[1 7]	Normal	Prolonged	Markedly diminished	Non-retractility of clot	Normal	Normal	Normal	..	..	Diminution in number of platelets and non-retractility of clot make diagnosis of purpura possible, even in absence of other features.
D. Chronic purpura[1 2 3 8]	Normal	May be prolonged	Diminished	Non-retractility of clot	Normal	Normal or increased	Normal	..	Negative	
II. Secondary hemorrhagic disease.										
1. Blood diseases. A. Aplastic anemia[3 9]	Prolonged	Prolonged	Diminished	Diminished	Diminished	Normal or increased	Normal	..	..	Coagulation time and bleeding time both prolonged (compare with hemophilia).
B. Leukemia[3 8 9]	May be prolonged	Normal or prolonged	Normal or diminished	Normal or diminished	Normal	Increased	Slightly diminished	..	Negative or positive	Platelets diminished in lymphatic leukemia; increased in myeloid leukemia; fibrinolysis present in myeloid; absent in lymphatic leukemia.[10]
2. Hepatic disease. A. Cirrhosis of liver[6 8 11]	Normal	Prolonged	Normal	Normal	Normal	Normal	Diminished	Normal	Positive	The prolonged bleeding time in cirrhosis with hemorrhagic symptoms is due to the fibrinogen deficiency; the clot is too soft to close the ruptured vessels.
B. Cholemia obstructive (without liver injury)[3 12 13]	Normal or prolonged	Normal	Normal	Normal	Normal	Normal	Normal	Diminished	..	Blood calcium may be present in excess but it is bound by bile pigment and is unavailable for prothrombin activation.
C. Cholemia (with liver injury)[3 9]	Prolonged	Normal or prolonged	..	..	Normal or diminished	Increased	Normal or diminished	Normal	May be positive	Terminal drop in prothrombin noted in one instance;[3] prothrombin may be diminished in congenital family jaundice and in congenital stenosis of bile ducts.[3]
3. Infections and intoxications (symptomatic purpura): septicemia, typhoid, tuberculosis, chloroform poisoning[3 6 9]	Normal or prolonged	Normal or prolonged	Normal or slightly diminished	Normal	Normal or diminished	Increased	Normal or diminished	Normal	..	Bleeding time prolonged in chloroform poisoning due to fibrinogen deficiency; platelet count may be diminished during acute stage of infections;[7] prolonged coagulation time and bleeding in in septicemia due to antithrombin excess.

*The numbers refer to the papers listed in the bibliography. The facts compiled in this table are based upon the data obtainable from these investigations.

this group by the methods outlined, I have endeavored to find out whether these could be differentiated one from the other by the *in vitro* tests without resorting to a differential diagnosis based upon clinical symptomatology. A glance at the tabulated results will show that such a laboratory diagnosis as opposed to a clinical diagnosis can readily be made in those disease types at least which most frequently come to the attention of the clinician. It is possible to group the diseases studied according to the essential abnormality in the coagulation complex, although it must be kept in mind that when carefully studied, some of the conditions under consideration may show a defect in more than a single factor of coagulation.

Platelet Group. Duke[7] in particular has emphasized the relationship of the blood platelets to hemorrhagic disease. And there can be little doubt that a diminution of these elements is directly responsible for the hemorrhages observed in purpura hemorrhagica and in some, but not all, types of chronic purpura. For thorough analyses of the blood, especially in purpura hemorrhagica, has shown the other factors of coagulation to be present in normal amounts. One might, of course, enter into a lengthy discussion concerning the manner in which platelets act in blood coagulation, but such speculations would lead one too far afield. Duke has laid emphasis upon the mechanical action of blood plates and their ability to stop hemorrhage by the role they play in the formation of thrombi. Others believe that platelets also facilitate clotting through their chemical action, for, as is well known, platelets are an important source of prothrombin and a thromboplastic substance which hastens coagulation by neutralizing the antithrombin present normally in the circulating blood. According to this view, platelets bear a more intimate relationship to the other factors concerned in blood coagulation. Doubtless both conceptions of the function of platelets is correct, and their importance rests both in their agglutinative power as well as in their content of prothrombin and thromboplastin.

It is well, then, to bear in mind that one type of hemorrhagic disease (acute and chronic idiopathic purpura hemorrhagica) may be attributed to an extreme reduction in the number of platelets. Furthermore, evidence that the platelets bear a direct relationship to the hemorrhages in this group comes from the observation that relief of the tendency to bleed follows not only the rise in the platelet count occurring at a remission of the disease, but following the increase in platelets brought about by transfusion. The value of transfusion in the treatment of the purpuric diseases will be considered in the paragraphs on treatment.

The prolonged bleeding time and non-retractility of the clot, which occur with such constancy in this group, are directly dependent upon the platelet deficiency. Only one other group of conditions shows so marked a prolongation of the bleeding time,

namely, the diseases associated with a reduced quantity of fibrinogen. In this instance prolonged bleeding is striking only if the reduction is extreme.

Prothrombin Group. The results of experimental and clinical studies obtained thus far give strong support of the existence of a group of conditions in which hemorrhage may be attributed to a deficiency of prothrombin. There can be little doubt that the hemophiliac condition, both in the true hereditary type of the disease and in those instances in which the disease arises *de novo* without a definite history of heredity, is due to diminution of this element. In fact, this property of hemophiliac blood is so striking that it distinguishes hemophilia at once from other hemorrhagic conditions and serves as a convenient method of making a diagnosis of hemophilia *in vitro* even in the absence of any proved history of the existence of the disease in the patient's antecedents.

In this same group belongs also hemorrhagic disease of the newborn (morbus maculosus neonatorum). Whipple has studied a type of this disease (melena neonatorum) in which there was a complete disappearance of prothrombin from the circulating blood. And more recently we have observed at the University of California Hospital an instance of hemorrhagic disease of the newborn with profuse bleeding from the umbilicus in which a similar defect was demonstrable.[4] There is some evidence that prothrombin may be present at birth but vanishes during the first few days of life.[15] It would seem that the function of the tissues and organs concerned with the elaboration of prothrombin in these cases is not yet in stable equilibrium, and this may account for the success following the intravenous injections of whole blood in tiding over a period of hemorrhage which would otherwise prove fatal.

In still another disease group—the aplastic anemias—the cause of the bleeding tendency is due in part at least to a prothrombin deficit. Unlike hemophilia and hemorrhagic disease of the newborn it has been possible to show that in aplastic anemia a diminution of the blood platelets is also an important cause of the hemorrhages. It is of interest that in this disease we have definite evidence of the existence of a hypofunctionating marrow, so that it may be contended that the aplastic marrow may be partly responsible for the lack of certain of the factors of coagulation. That this is true has been proved by recent experiments. Hurwitz and Drinker[16] have shown that coincident with the drop in blood platelets following marrow injury by benzol there is also a drop in circulating prothrombin, and more recently Drinker[17] has shown by actual profusion of the bone marrow that it contains prothrombin. It would appear, therefore, that the hemorrhagic features of the aplastic type of pernicious anemia are directly secondary to a definite deficiency of the bone marrow.

Antithrombin Group. This group consists of a number of heterogeneous clinical entities. Although it is permissible to place them under this heading, because an antithrombin excess is the chief cause of the pathological hemorrhages associated with these various diseases, it should be emphasized that this is not the only demonstrable defect in the coagulation elements. Thus certain chronic purpuras in which the hemorrhagic symptoms may be due to periods of antithrombin excess also show moderate diminution of blood platelets with the attendant phenomena of prolonged bleeding time and non-retractility of the clot. Of the other blood diseases, cases of aplastic anemia may at times show an excess of this element, although this was not true of the patient studied by us. The leukemia patients, too, have been shown to have an excess of antithrombin in their blood during the periods of active hemorrhage, but they also may have a deficiency in other factors—platelets or fibrinogen.

According to the best evidence, an excess of antithrombin may occur with greater constancy in diseases of the liver or in infections and intoxications producing liver injury. Thus far an antithrombin excess has been demonstrated to be the cause of hemorrhagic symptoms in icterus associated with liver injury. This is also true in certain cases of septicemia, typhoid fever, and miliary tuberculosis. These clinical observations confirm the experimental studies, which seem to indicate that the liver may be concerned with the production of antithrombin.

Fibrinogen and Fibrinolytic Group. Here belong, for the most part, those diseases associated with acute or chronic liver injury. The fibrinogen of the blood may be greatly reduced by various poisons, such as chloroform[18] and phosphorus, which injure the liver. In severe poisoning the fibrinogen may reach a very low level. A deficiency in this element explains the hemorrhagic features and the prolonged bleeding time of these intoxications. The blood coagulates, but the clots are too flabby to close the ruptured capillaries. Whipple believes that a similar explanation may be offered for the hemorrhagic tendency observed in acute yellow atrophy and in yellow fever.[15]

Of the chronic liver diseases which may show a low fibrinogen content of the blood, liver cirrhosis is the most important. It should be emphasized that a marked decrease of fibrinogen in this condition is not of constant occurrence, but when the content is low it is of grave prognostic import.

A ferment capable of giving rise to hemorrhagic symptoms by dissolving the fibrin of the clot has been demonstrated in liver diseases and more especially in hepatic cirrhosis with insufficiency. It has also been demonstrated in the blood of certain types of myeloid leukemia, and it has been suggested that its absence in the lymphatic type of leukemia may serve as a means of differentiating the two types *in vitro*.[10]

Calcium Group. Thus far no experimental proof has been brought forth that a deficiency in calcium salts is responsible for any form of hemorrhage. It has already been pointed out that the prolonged coagulation time in obstructive jaundice without liver injury is not due to a diminution in the calcium content of the blood, but rather to its unavailability for coagulation. From a practical view-point, however, an actual or a functional deficiency of calcium would lead to the same symptoms, and the therapeutic indications would therefore be the same. These will be considered in the paragraphs on treatment.

Other Factors. Only little work has as yet been done upon the significance of deficient thromboplastin formation. Whether or not a deficiency in this substance may give rise to a hemorrhagic tendency is difficult to determine at present because no direct method of studying this factor exists. Some information concerning this substance as it exists in the blood can be obtained by an enumeration of blood platelets. But information obtained from this source is incomplete, inasmuch as all of the formed elements of the blood and other tissues have been shown to possess thromboplastic properties to a greater or less extent. Sahli has indeed maintained that in hemophilia there exists a thromboplastin deficiency (fermentative inferiority) of the protoplasm of the body, whereas others have localized it partly in the blood platelets.[19]

The Treatment of Hemorrhagic Diseases. *General Treatment.* Although one must admit that as regards a specific therapy the elaborate studies described have contributed little, they have, however, made possible a more rational and a more critical treatment of hemorrhagic conditions. In the paragraphs on treatment I purpose to consider separately the principles underlying the general and local measures recommended, and of the former only those whose value has been tested by experiment. Apart from all other considerations it seems fair to assume that a therapeutic measure employed for the general control of hemorrhage is successful only if it causes a cessation of the bleeding, and so affects the disease process itself that the coagulability of the blood is increased. On the basis of such criteria only a few of the measures advocated can be said to possess real value.

Calcium Therapy. Although clinical reports as to the value of this method of treatment have been conflicting, the general idea has been widely accepted that the coagulation time in disease can be shortened at will by giving the proper dose of calcium. The great popularity which this form of treatment has received in the control of the hemorrhages of hemophilia and other bleeding conditions is largely due to the publications of Sir A. E. Wright. He was among the first to call attention to the need of an accurate method of obtaining clinical data on blood coagulability as a rational basis of therapeutics in this group of diseases. And by testing the

coagulation time with a series of capillary tubes before and after the ingestion of calcium salts, Wright arrived at the conclusion that calcium administered in repeated doses by mouth can render the blood more coagulable.

In general the contentions of Wright have not gained support from the work of later investigators. In 1909 Addis[20] by using a modification of McGowan's method of determining blood coagulability, reported a careful series of experiments on the effect of calcium salts on the blood in various types of disease. From these studies he concluded that calcium salts are unable to effect any change in the coagulation time of the blood. Indeed, all subsequent experimental as well as clinical observations have confirmed his findings so far as hemophilia is concerned. According to the best experimental work there is only one condition in which calcium feeding is indicated, namely, in obstructive jaundice with a delayed coagulability of the blood. Both Schloessmann[21] and very recently Lee and Vincent[13] have observed a shortening of the coagulation time following the administration of calcium in this condition. Lee and Vincent point out that to be effective calcium must be administered in large doses (100 grains a day), and must be given over a period of several days before any marked effect on the coagulation time is seen.

Serum Therapy. This form of treatment has gained remarkable popularity since Weil, in 1905, reported the successful therapeutic results following the use of serum in hemophilia. The author feels that while the question of the usefulness of serum or any other remedy for the constitutional treatment of these disorders must in a measure be determined on the basis of clinical results, that too little attention has been paid to the evidence gained from well-controlled experiment. Instead of narrating the clinical successes and failures which have attended the use of serum I prefer at this time to call attention to some observations and experiments concerning the use of serum which most clinicians and writers on this subject usually fail to mention.

The essential coagulation-accelerating substance contained in fresh serum is thrombin. In addition it may contain a small amount of thromboplastin, liberated by the disintegration of cellular elements, and some antithrombin which is present in small amounts in all sera and bloods. It should be emphasized that old serum differs markedly from fresh serum in the following respect: On standing a few days the thrombin of the serum is converted into an inactive form—metathrombin—so that old serum contains less thrombin and more antithrombin. Because of this transformation it can actually be shown by *in vitro* tests as well as by subcutaneous and intravenous injections into animals and man that old serum *retards* rather than *hastens* the clotting of blood not only in normal animals but also in pathological conditions like hemophilia.[21] On the basis of these experimental studies we believe that old serum—anti-

diphtheritic and the like so commonly employed in the treatment of hemorrhagic conditions—should be entirely discarded.

And if we adhere to the criteria which should guide our judgment as to the value of a therapeutic measure in checking constitutional hemorrhage it is not possible to make any greater claims for fresh serum. It is true that an extensive literature has accumulated in support of the usefulness of this measure in a host of conditions manifesting a bleeding tendency, but in only a few instances have the observations been controlled by studies upon the blood coagulability before and after the serum injections. In fact, where careful experiments to determine this point have been carried out they have demonstrated the lack of value even of fresh serum.

Concerning the value of serum in the disease groups which have been considered above, one may say with considerable certainty from the searching experiments of Schloessmann and a number of other workers (Sahli,[23] Baum,[24] and Ottenberg and Libman)[25] that serum injections have little if any effect on conditions due to a prothrombin deficiency, hemophilia, and hemorrhagic disease of the newborn. Schloessmann was able to show conclusively that no immediate or delayed increase in the coagulability of the blood resulted following the subcutaneous or intravenous injection of fresh serum into hemophilic patients. Nor has serum yielded brilliant results in the platelet group of diseases—the purpuras; whereas in them the use of whole blood has been of the greatest value in bringing hemorrhage to an early arrest. The reason for this will be discussed in the paragraphs on the therapeutic value of whole blood. Moreover, it is obvious that the use of serum would be valueless where the faulty coagulation depended upon an absence or a deficiency of fibrinogen, and that the use of old serum would be contra-indicated in the group in which the hemorrhagic tendencies were attributable to an excess of antithrombin. In fact, Howell has shown that following the intravenous injection of fresh serum or thrombin the antithrombin may even show an increase a few hours after such injections, although the balance quickly returns to normal.

In the light of these facts it is a little difficult to explain the enthusiastic claims which have been made for serum therapy in the literature. Doubtless serum does at times give remarkable hemostatic results in some cases of hemorrhage, and this is in harmony with the striking coagulation-accelerating action of serum on whole blood in the test-tube. The manner in which serum may produce such favorable results *in vivo* is as yet not clear, although it must be evident from what has been said that injections of serum do not increase the coagulability of the blood. And in fact the development of improved methods of administering whole blood in the treatment of hemorrhagic conditions and the brilliant results attending its use is gradually causing some of the enthusiasm for serotherapy to wane.

Whole Blood. Obviously, the most ideal therapy would consist in supplying to the patient the element in which his blood is lacking, or in neutralizing those substances which may be present in excess. Unfortunately, such a mode of treatment is not possible in the present state of our knowledge. In the absence of a specific therapy the use of whole blood which contains all of the factors concerned in clotting appears to be most logical, and, in fact, remarkable success has attended its use in the hands of a large number of clinicians. It is not my intention to recount the numerous methods which have been advocated for the administration of whole blood, but to dwell rather upon the principles underlying this form of treatment.

The number of instances in which the use of whole blood has yielded brilliant therapeutic results have increased greatly during the past few years; but unfortunately only a few of the recent reports contain observations on the blood coagulability before and after such therapy, so that we do not know just how whole blood produces its favorable results. Those cases which have been studied from this view-point, however, have given us some interesting facts concerning the effect of whole blood upon the factors of coagulation in a few disease groups which, I believe, deserve brief consideration.

According to the clinical observations of Ottenberg and Libman, transfusion may be looked upon as a specific therapy for the control of the hemorrhages in hemophilia. In fact, they go so far as to recommend that "every individual known to have hemophilia ought to have at his command several persons whose blood by previous tests is known to be compatible with his . . . ."[25] So far as the author is aware, experiments have not as yet made clear the reason for this specific action of whole blood in hemophilia. But a little insight into its probable action has been gained from experimental studies on the influence of blood in hemorrhagic disease of the newborn, which as has been pointed out also belongs to this group of conditions associated with a prothrombin deficit. In a case of hemorrhagic disease of the newborn, which recently came under our observation,[4] it was found by blood studies that the essential defect in the process of coagulation was due to a deficiency of prothrombin, which probably accounted for the excessive bleeding from the umbilicus. Having tried local hemostatics without good effect, resort was finally had to the injection of whole blood into the longitudinal sinus through the anterior fontanel. After the injection of 40 c.c. of blood the hemorrhage ceased almost instantly and a study of the blood about six hours later showed a normal coagulation time and a normal prothrombin content. This experience is cited in detail because we know from experiment that in this case a restoration of the prothrombin balance was effected, either by a stimulation of the tissues concerned with the elaboration of this

substance or by the actual addition of this substance to the circulating blood.

Furthermore, experiment has shown that transfusion of whole blood is also especially indicated in another clinical condition in which both the circulating prothrombin and the blood platelets are deficient, namely, aplastic anemia. Drinker and I[8] have followed such a case for over eight weeks. Each time following transfusion there was prompt cessation of bleeding from the gums, and, as studies of the patient's blood showed, there was also an increase in the platelet count and in the prothrombin. To be sure the improvement was only temporary, but the administration of whole blood tided the patient over the immediate dangers of prolonged hemorrhage.

In the platelet group of hemorrhagic conditions—the purpuric diseases—transfusion has been found to be the only logical method of combating hemorrhage. Transfusion of blood in this group of hemorrhagic diseases has been especially recommended by Duke.[7] This worker has shown by a study of the blood before and after transfusion that both the bleeding time and the number of platelets may become normal after this procedure. In two out of the three cases which he cites the platelet counts before transfusion were 3000 and 20,000; the bleeding times were respectively ninety and twenty minutes. After transfusion the counts were 110,000 and 89,000, and the bleeding time in each case was three minutes (normal). After the disappearance of these platelets, apparently introduced into the patients' circulation by transfusion, the bleeding times became forty and twenty minutes. But none of the patients showed so marked a tendency to bleed after transfusion as before, even after the platelet counts had dropped to their previous low level. It would appear, therefore, that platelets introduced into the blood stream in this way rapidly disappear. In these two instances there was complete relief from hemorrhage for three days after transfusion.

Ottenberg and Libman are equally enthusiastic over the therapeutic results of blood transfusion in purpura hemorrhagica. They report twelve transfusions in 9 patients, with complete recovery in 6 cases. Not only do they emphasize that transfusion produces a prompt cessation of the hemorrhages in most of these cases, but they believe that it also has some curative action, the exact nature of which is not entirely clear. That it has some connection with the fresh supply of blood platelets seems likely, but all the benefits produced cannot be accounted for in this way, for the normal life duration of platelets is known to be very short. It is not unlikely that some of the favorable action of whole blood may be attributed to the effect which it may have in stimulating the regeneration of thromboplastic substances (platelets). This view has some basis in experience because, as Emsheimer[26] and others have found, small

intramuscular injections of whole blood in purpura hemorrhagica are as efficient in controlling bleeding as are large transfusions, and it cannot be assumed that small intramuscular injections exert their influence by direct action.

Other Measures. There is one other form of general treatment which has been subjected to experimental study, and which therefore deserves brief mention. Some workers, especially Schloessmann,[21] have tested the effect of intravenous injections of saline extracts in hemophilia, and Hurwitz and Lucas[2] have made observations upon the effect of intramuscular injections of the brain phosphatid—*kephalin* on the coagulability of the blood in hemophilia. All of these studies have demonstrated the ineffectiveness of this form of therapy. The reason for these failures is not far to seek. As Howell has shown, solutions of pure thrombin or serum containing thrombin and thromboplastin may be introduced into the circulation in quantities that in the test-tube would cause rapid and firm clotting and yet no harm be done. It is apparent, therefore, that a healthy animal, and probably also an individual having pathological hemorrhages, may exhibit a protective response against the effects of substances which would endanger life by the formation of intravascular clots. The nature of this defensive reaction consists, it is thought, in the formation within the organism of a compensatory amount of antithrombin to bind either the injected thrombin or to neutralize the tissue extracts introduced into the circulation. This hypothesis would explain the results which we obtained following the intravenous injections of kephalin solutions into animals. The immediate effect of intravenous injections was an increase in the coagulability of the blood. This increased coagulability was only transitory, however, and was followed soon by a return of the blood to a normal state, or in a few instances by a decreased coagulability. In hemophilic patients we could demonstrate little change in the blood after intramuscular injections of kephalin. As to the effect of intravenous injections we have no data to present, because we did not feel that the intravenous injections of tissue extracts were entirely devoid of danger.

Local Treatment. It has been my purpose in this paper to deal more particularly with the general treatment of pathological hemorrhage, but it may be worth while to say a word in regard to one or two measures which have proved to be of value in the treatment of uncontrollable hemorrhage from external wounds so frequently met with in hemorrhagic conditions.

Of the measures recommended for the control of external bleeding it would appear that the local injection of whole blood, defibrinated blood, and of serum into the tissues about the bleeding surface have all given good results. Whole blood and defibrinated blood are to be preferred because they contain cellular elements which upon disintegration furnish a coagulation-accelerating substance or

thromboplastin (also designated "zymoplastic" or "thromboplastic substance"). For these reasons tissue extracts rich in thromboplastin have long been employed.

To such an extract prepared from brain tissue reference has already been made in the paragraphs on general treatment. Kephalin can be prepared according to the method of Howell.[28] It is soluble in ether, but insoluble in alcohol, acetone, and water. In the latter it forms a milky emulsion. Unlike saline or aqueous extracts it can be sterilized without weakening its action. Howell has called attention to this difference between saline or aqueous extracts and ethereal extracts. He has shown that heating the former precipitates the protein together with the active phosphatid; whereas if the phosphatid is first extracted with ether the residue may be dissolved in water and the emulsion thus obtained is unaffected by boiling.

The various preparations of kephalin obtained may be standardized by testing their action on specimens of blood *in vitro* or by determining their coagulation-accelerating effect upon mixtures of oxalated plasma (fibrinogen) and fresh serum (thrombin). In this way we have become convinced that *in vitro* even high dilutions of kephalin will markedly accelerate the clotting of blood. The details of these tests will be recorded at a later date.

Clinical studies have shown that kephalin exerts an equally potent hemostatic action when brought into contact with wounded tissues. From our observations on hemophilia we have become assured that kephalin applied locally to the bleeding wounds of hemophiliacs brings hemorrhage to an early arrest.[2] And a number of reports[29] have appeared recently testifying to its great value also when applied to oozing wounds or hemorrhages from bone, kidney, muscle, and other tissue surfaces.

SUMMARY AND CONCLUSIONS. The clinical and experimental work of recent years has made possible a more logical classification of hemorrhagic diseases. Although it may be premature to speak of an etiological classification, more emphasis should be laid upon the experimental studies thus far carried out in the grouping of these conditions.

On this basis we may group a number of etiologically heterogeneous diseases about some defect or defects in the factors concerned in blood coagulation. Although more than one element may show an abnormality, it is permissible to designate these groups according to the essential defect present. And we may speak of a platelet group or a prothrombin group and the like, meaning that a lack of platelets or a deficiency of prothrombin is in the greatest measure responsible for the pathological hemorrhages observed.

In the study and in the grouping of hemorrhagic diseases a number of methods are now available which because of their simplicity possess great clinical value. And we believe that every instance of

obscure hemorrhage should be studied by these methods for the purpose of finding out whether the cause is attributable to an abnormality in blood coagulation. As has been pointed out, some of the tests have great practical importance in diagnosis and treatment. It may be well to emphasize that the existence of a hemophiliac condition ought to be excluded by *in vitro* tests preliminary to any operation upon a patient exhibiting the hemophiliac tendency.

Greater attention should be paid to experiment in determining the value of therapeutic measures in the constitutional treatment of hemorrhage. Observations on the clinical improvement and on the cessation of hemorrhage after treatment should be supplemented by studies upon the clotting time of the blood and the factors of coagulation before and after the institution of such therapy. In this way it will be possible to arrive at a more rational treatment of these cases.

Tested by such criteria, whole blood, we believe, is at present the most logical and most efficacious therapeutic agent for the control of bleeding in the greatest number of patients showing hemorrhagic tendencies. In the majority of instances calcium therapy has not yielded good results and the value of serum treatment has been much overemphasized.

Of the local hemostatic agents recommended, kephalin gives promise of being an important adjunct in the treatment of bleeding from external wounds. It is to be hoped, therefore, that this tissue extract will prove of real value in the control of the immoderate hemorrhages from the wounds which so frequently complicate the hemorrhagic diseases.

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COLON BACILLUS PYELITIS CONSIDERED WITH REFERENCE TO CASES IN BOY SUBJECTS.

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Laruelle and Tavel, in 1889, first found the colon bacillus in the living subject outside the intestinal tract.[1] In 1893 Park[2] made a review of the literature on this subject and assigned to Welch[3] and Councilman credit for the name "colon infection," and to Clado and Albarran priority for classifying Bacillus coli communis as a urinary pyogenic organism (Rawls).[4] The importance of urinary infections in children was first emphasized by Escherich in 1894, but the prevailing form was considered by him to be a cystitis.[5] A few months later Holt[6] reported three cases which he described as those of pyelitis. Since then the literature has been steadily augmented until the subject of colon bacillus infection of the urinary tract has become one of the most common under study. Particularly, the importance of this type of infection in children is gradually receiving wider recognition.

Occurrence and Pathogenesis. Bassler[7] found colon bacilli in the urine of 9 per cent. of 191 adults having no urinary symptoms or constitutional disturbances, and therefore expressed the view that the organism may exist in the urine without active prolifera-

[1] Rawls, R. M.: Bacillus Coli Infection of the Urinary Tract, New York Med. Rec., October 7, 1911, p. 709.
[2] The Importance to the Surgeon of Familiarity with Bacillus Coli Communis.
[3] The Bacillus Coli Communis: The Conditions of its Invasion of the Body and its Pathogenic Properties, Med. News, December, 1891.
[4] Loc. cit.
[5] Escherich, Theodore: Prog. Med., 1914, p. 138.
[6] Arch. Pediat., November, 1914.
[7] Innocent Colon Bacilli in Urines, New York Med. Rec., July 6, 1912.

tion and practically without injurious effect. The possibility that this bacillus may thus inhabit the urinary tract of a child without at some time causing serious effects will seem doubtful to many; and yet cases in children who have passed through the acute febrile stage of pyelitis and continue to show the excretion of bacteria and even pus, over a period of months, but without clinical symptoms, are extremely common.

The predominance of urinary infection in girls has long been recognized. Cnopf reports that of 40 children who had colon cystitis associated with enteritis, 8 were girls.[8] Elterich[9] saw 19 cases of urinary infection during a period of two years, in children between the ages of seven and a half months and eight years; and all of the patients were females. Of 26 cases reported by Still,[10] 23 occurred in girls. In 1911–12 cases of pyelitis and pyelocystitis comprised 5 per cent. of all the admissions at the Children's Hospital at Freiburg, and 95 per cent. of the patients in this group were females.[11] Statistics upon this phase might easily be multiplied, giving ground to the view that the infection is most frequently transmitted by direct extension upward through the lumen of the urethra, and that the other two modes of transmission (hematogenous and transparietal infection) are exceptional. On this point, however, the recent work of Eisendrath and Kahn,[12] showing the role of the lymphatics in ascending renal infection, is definitely convincing. The infection most frequently progresses upward through the lymphatic capillaries by way of the submucosa of the bladder and the peri-ureteral sheath. The close anatomical relationship of the rectum and urethra in the young female is quite probably of greater importance in this transmission of bacteria than the mere proximity of the anal and urethral orifices. Wieder found that colon bacilli injected into a rectum which had previously been traumatized could be recovered from the bladder. In this connection, moreover, the possible agency of the thread-worm in conveying bacteria from the rectum to the urethra and bladder has been remarked; while Langstein[13] has called attention to the frequency of pyelitis as a sequel of Hirschprung's disease.

Without entering further into a consideration of the etiological and pathological factors concerned, I desire especially to call attention to the clinical possibilities presented by urinary infection in the male child, and to this end offer records of three such cases.

[8] Clarence A. McWilliams: Infections by the Bacterium Coli Communis, with Particular Reference to the Urinary Tract, New York Med. Rec., July 7, 1906, p. 7.
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[13] Med. Klinik, 1913, No. 37.

CASE REPORTS.

CASE I.—H. A., five years old and the youngest of three children, has a negative family history and had been free from serious illness prior to the development of the condition which is the subject of this report. He had, however, always been delicate in appearance, and for several weeks preceding this illness had appeared "pale and poisoned-looking."

Case I. Rash recurrent during the course of pyelitis.

Early in January, 1915, this patient developed slight puffiness of the face, and simultaneously an eruption of irregularly outlined reddish macules ranging in area from 1 to 20 to 30 sq. cm., slightly elevated, and distributed over the face, entire trunk, and extremities, with the exception of the palms and soles. The more typical fresh lesions were circinate. This rash persisted without complete disappearance, the lesions fading and reappearing in successive crops, throughout a prodromal period of about three weeks, with no

accompanying symptoms other than mental irritability, pallor, and obstinate constipation. By the expiration of this period the patient had developed a septic type of temperature ranging from 99° to 103°, headache, pain in the back (especially the right lumbar region), soreness and stiffness of the legs (prohibiting standing and passive extension), and a cough suggestive of pertussis.

All of the signs and symptoms persisted without significant abatement until February 21, at which time a correct diagnosis was made possible by telephone as a result of the well-grounded refusal of the patient's attending physician to reconcile the symptom-complex with any other primary condition than intestinal toxemia, notwithstanding the fact that miliary tuberculosis, grippe, whooping-cough, typhoid fever, meningitis, otitis, and poliomyelitis had all received the consideration of those in attendance. It was thus suggested that the examination of the urine, which had been for the most part chemical, be supplemented by repeated searches for pus and bacteria, that a blood smear be examined to exclude the possibility of the presence of trichinosis, and that pending positive findings, urotropin be administered. Thereupon the urine was found to contain "pus cells" to the number of about 100 per field (low power), and a heavy cloud of bacteria. (There was no eosinophilia.)

Hexamethylenamin was administered in doses of 20 grains daily, in conjunction with acid sodium phosphate, and within three days the temperature had subsided, and the constitutional symptoms had abated. After about ten days, however, the skin eruption, which had mostly disappeared, again became marked; the urine, which had been fairly free from pus, was observed to be dark brown and turbid, and the temperature rose to 103°, persisting at this as a maximum, with remissions to 100°, during the succeeding five days.

Physical examination March 7 was practically identical with that recorded at Roosevelt Hospital March 31 (see below).

Blood: Leukocytes, 17,000; polynuclears, 56 per cent.; mononuclears, 33 per cent.; eosinophiles, 1 per cent. Agglutination test with three strains of Bacillus coli communis negative.

Urine: Very cloudy; slightly acid; specific gravity, 1014. Albumin present in a very faint trace. Microscope reveals a few hyaline casts, many pus cells closely adjacent and in clumps, and numerous bacilli. Culture of a specimen aseptically collected shows pure growth of Bacillus coli.

The hexamethylenamin and acid sodium phosphate were now discontinued, and an "A B C" mixture combining acetate, bicarbonate, and citrate of potassium was administered in dosage aggregating 60 to 80 grains daily. The temperature subsided within thirty-six hours and remained subnormal throughout a second period of improvement, during which the urine was alkaline and free from

pathological sediment except for the presence of many bacteria and about 20 pus cells per field.

An attempt at the end of ten days to replace the alkali by "amphotropin" in dosage of 15 grains daily was promptly abandoned because of the observation that within forty-eight hours the urine had again become strongly acid and contained occasional red blood cells. Moreover, before the alkali could be resumed the patient had a recurrence of acute symptoms, including the rash and a temperature of 104°; and on the night of March 26 this attack culminated in cardiac weakness and partial collapse. At the end of four days, however, following stimulation and an initial dose of vaccine prepared from the culture of March 7, sufficient improvement had taken place to warrant his removal, a distance of 200 miles, to Roosevelt Hospital.

Physical examination upon admission March 31 was negative except for the following points:

"Child is poorly developed, pale, and looks chronically ill. Lymph glands: postcervical and axillary 'shotty.' One or two bean-sized inguinal. In left lower abdomen are a number of bean-sized masses, discrete, freely movable, not tender, which seem to coalesce with the inguinal group and are palpable deeply, extending upward to the level of the umbilicus. Skin moist. On both legs are many circinate, macular lesions."

During a stay of three months in the hospital this patient was given two courses of autogenous vaccine, comprising a total of fifteen injections in dosage which was increased from 25,000,000 to 180,000,000 organisms. The vaccine apparently produced no untoward effects, but its value in this instance may be regarded as unproved because of the recurrence of temperature ranging from 101° to 104° over three separate periods of five days each before discharge of the case. On one of these occasions tenderness over the right kidney was noted coincidently with a leukocytosis of 34,000 and a polynucleosis of 92 per cent.

Relapses, indicated by a return of the fever, were invariably attended by increased acidity of the urine, even during the administration of large doses of alkali, which was given steadily either in the form of potassium citrate (40 to 50 grains daily) or in that of the "A B C" mixture supplying a combined total of acetate, bicarbonate, and citrate ranging from 135 to 270 grains daily. An acid reaction persisted on one occasion (April 29 to May 19), when the dosage of the "A B C" diuretic was as high as 270 grains. The acidity in terms of decinormal sodium hydroxide varied during this period from 24 to 0.04 c.c., averaging 6.55 c.c. Following the discontinuance of the alkali the average acidity during the next five days rose to 20.4 c.c., falling to 6.14 c.c. upon the resumption of the alkali in dosage of about 150 grains daily. For several weeks before the patient's discharge, calcium lactate was given to the

amount of 24 grains daily in conjunction with the sodium citrate, which was maintained at 30 grains daily, on the assumption that the calcium might be less depressing, less productive of fluid retention, and possibly of more favorable influence on the cutaneous eruption than the sodium and potassium salts when given exclusively. The average acidity for a typical nine days of this period was 30.4 c.c.

This boy gained 4½ pounds during his hospital stay, and has remained in fairly good health during the two years following his return home, but at various times he has had a temperature ranging from 100° to 101°, mild outbreaks of the characteristic rash, and a slight degree of pyuria.

Case II.—J. H. F., aged ten years, the second of three children, with negative parental history, had whooping-cough at two years and measles at four years. Pin-worms had been noted, and eneuresis had always been annoying. In general, however, his health had been good.

June 30, 1914, this boy was brought to Vanderbilt Clinic for treatment of chronic eneuresis, cough which had been recurrent over the period of a year, anemia, and loss of weight.

On physical examination he was found to be fairly well developed, but pale and listless, with a temperature of 101°. The tongue was heavily coated and the breath offensive. The tonsils showed moderate enlargement, the breathing was abnormally oral, and the cervical lymph nodes were palpably enlarged. Auscultation of the chest detected many coarse rales, most numerous at the base of the right lung. Those heard low in the right axillary region were thought to be pleuritic.

The only diagnoses offered to explain these findings were (1) pulmonary tuberculosis, and (2) bronchopneumonia accompanied by pleurisy with a small effusion in the right thorax. A von Pirquet test proved negative. Fever was not noted after July 3, and in the period up to August 19 the patient's general condition slowly improved, although the cough and physical signs referable to the right chest persisted in lessened degree for about three weeks. The weight observations were: June 30, 52¼ pounds; July 15, 53 pounds; July 23, 54 pounds; August 5, 55¼ pounds; August 19, 55 pounds. On the last date the patient passed from observation in apparently good condition and was not seen again until October 5. In the interval his health improved and the weight increased to 58½ pounds, although cough continued annoying in the morning. When seen two weeks later, however, he was distinctly ill, having had bronchitis for several days and lost 5½ pounds. His temperature was 101.6° and rales were again heard throughout the chest, especially at the old location in the right axilla. The von Pirquet test was repeated, but was again found negative. In the next few days the cough subsided, and a radiograph October 23 failed to reveal any intrathoracic lesions.

At this time attention was again directed to the eneuresis; and upon routine examination preparatory to treatment the urine was found to be turbid from the presence of pus which filled the entire microscopic field.

Treatment with hexamethylenamin alternating weekly with sodium citrate was now instituted; and although the patient's attendance at the clinic was irregular and he did not report from November 23 to December 23, on the latter date the urine was found to be clear and free from pus. The improvement inaugurated apparently with this treatment continued without interruption, so that by the middle of January, 1915, he weighed 58¾ pounds (6 pounds more than on his first visit), and except for a moderate tendency to eneuresis, he had no complaints. He now passed from observation for a period of over three months.

May 12 a message was received from the patient's home stating that he had been ill for a month and was thought to be dying from pernicious anemia. He was found semicomatose, but suffering visibly from orthopnea and air hunger. The face and limbs showed only slight edema, but the combined symptoms were unmistakably those of uremia, and the existence of this condition was confirmed by examination, showing the presence of albumin in the urine in amount approximating one-fourth its volume. On the same night three convulsions supervened, one lasting over a half-hour. During May 13 and 14, however, following the giving of chloral and sodium bromide by the bowel and stimulation hypodermically with caffein and digitalis, combined with measures to promote elimination, there was unexpected improvement.

Throughout the next few days repeated examinations of the urine failed to afford findings essentially different from those of May 12. Despite the constant presence of albumin in large amount, the specific gravity remained between 1008 and 1015, and the sediment uniformly failed to reveal pus cells, blood, or more than a few granular and hyaline casts. For an acute nephritis with such marked albuminuria the specific gravity was unusually low and the pathological sediment unusually scanty.

May 21, after a week without appreciable improvement, the patient was removed to Roosevelt Hospital.

Physical Examination upon Admission. "A well-nourished boy, in appearance chronically ill, showing marked pallor of the skin and mucous membrane, but no dyspnea, cyanosis, or jaundice.

Eyes and ears negative.

Axillary and inguinal lymph nodes 'shotty.'

Chest normal in contour with good respiratory excursion.

Lungs clear.

Heart: Apex impulse in fifth space 8 cm. to left of median line. Cardiac dulness corresponds. Sounds at apex regular, slightly rapid, and of good quality. First sound is followed by a soft,

blowing, systolic murmur. There is a slight pleuropericardial friction sound. At the pulmonic area a soft systolic murmur precedes the pulmonic second sound.

Extremities show very slight edema. Knee-jerks normal. No Kernig."

June 2 the patient developed slight bleeding from the gums, and on June 7 vomited a little bright red blood. Drowsiness now became very marked and the breath took on an ammonia odor. Coma ensued without recurrence of convulsions and death followed on June 8.

The hospital chart records a retinal examination June 8, showing papillary edema and areas of exudation indicative of albuminuric retinitis, a blood culture the same day with no growth, blood-pressure ranging from 135 to 140 mm., phenolphthalein tests May 25 and June 2 showing respectively 10 per cent. and 0 dye excretion, and a special urine examination May 26 showing 139 mg. of non-proteid nitrogen per 100 c.c. of blood. In spite of these features the twenty-four hours' urine excretion recorded up to two days before death only once fell below 600 c.c., and the routine tests during the last six days invariably failed to show a specific gravity above 1012, or the presence of albumin, pus, or more than an occasional hyaline cast. Tests for acetone and diacetic acid during the last three days were also negative. A blood count June 3 showed: hemoglobin, 32 per cent.; red cells, 2,995,000; leukocytes 21,400; polynuclears, 77 per cent.; lymphocytes and large mononuclears, 18 per cent.; basophile cells, 2 per cent.; myelocytes, 3 per cent.; and many microcytes. The temperature was practically afebrile.

Autopsy was not granted.

The hospital diagnosis was "chronic uremia; chronic interstitial nephritis (glomerulonephritis); simple anemia."

Case III.—A. E., aged three and a quarter years, the first child of healthy parents, had purulent otitis media at one year of age, but thereafter was well until about twenty months old.

January, 1914, this patient had an attack of enterocolitis and developed convulsions which were followed by a period of fever not satisfactorily explained at the time, and lasting two weeks. A similar attack occurred the following March, also characterized by a convulsion, and accompanied by fever which persisted four days. At this time the urine was examined and found to contain pus.

Treatment with hexamethylenamin was given and prompt improvement ensued, but in the interval until August, 1915, there was a relapse every two or three months, with fever for a few days, and increase of the pyuria, which was never completely lacking even in the intervals between attacks. Hyaline casts were occasionally found, and on one occasion while taking the hexamethylenamin the patient had pain on micturition and slight hematuria.

In May, 1915, the administration of potassium citrate in dosage of 45 grains daily was begun and thenceforth continued at weekly intervals, alternately with the hexamethylenamin. The improvement which followed, however, was broken by relapses in June and July.

Physical examination August 8 showed the child to be slightly anemic, but in good musculature, weighing 31 pounds. The tongue was coated and the right tonsil was slightly enlarged. Cardiac examination detected slight impurity of the first sound as heard in the precordial region, but no organic murmur. The abdomen was unduly prominent. In other respects the findings were negative, except for the urinary examination. This revealed the presence of a moderate number of discrete pus cells.

The hexamethylenamin was discontinued and sodium citrate in dosage of 40 grains daily was prescribed in conjunction with culture of Bacillus Bulgaricus and syrup of the iodide of iron. This treatment was continued indefinitely, and three months after its commencement a report was received stating that the patient had had no relapse and was in better condition than at any time since the discovery of the pyelitis. A urine examination November 27, 1915, showed a very faint trace of albumin and a growth of staphylococcus (apparently due to contamination), but no pus or bacilli.

This case is of interest principally because of the existence of a temperature record kept faithfully by the boy's parents and based on observations morning and evening over a period of a year and a half. The report shows that there were seven distinct relapses of the pyelitis, each of which was productive of fever of 102° or higher, during the period of one year.

Significance of Pyelitis in Boys. Information derived from so small a group of similar cases is necessarily meager, especially since the chronicity of urinary infection of the type under discussion precludes the possibility of sufficiently prolonged individual observation in a given case. Certain general facts, however, seem worthy of special emphasis.

The finding of pus in a male child's urine (in the absence of a specific urethral discharge) should invariably suggest infection of the urinary tract by blood or lymph-stream absorption rather than by direct urethral contamination, which has been shown to afford a very inaccurate explanation of the occurrence of pyelitis, even in the female subject. Pyelitis in the male thus calls for the consideration of the possible existence of an intestinal focus or defect contributing to the escape of the colon bacillus from its normal habitat; and furthermore, pyelitis under these conditions should at least suggest the possibility of colon bacillus septicemia.

Of more practical value is the lesson that in cases of obscure fever in boys as well as girls, microscopic examination of the urine

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Case III.—A. E., aged three and a quarter years, the first child of healthy parents, had purulent otitis media at one year of age, but thereafter was well until about twenty months old.

January, 1914, this patient had an attack of enterocolitis and developed convulsions which were followed by a period of fever not satisfactorily explained at the time, and lasting two weeks. A similar attack occurred the following March, also characterized by a convulsion, and accompanied by fever which persisted four days. At this time the urine was examined and found to contain pus.

Treatment with hexamethylenamin was given and prompt improvement ensued, but in the interval until August, 1915, there was a relapse every two or three months, with fever for a few days, and increase of the pyuria, which was never completely lacking even in the intervals between attacks. Hyaline casts were occasionally found, and on one occasion while taking the hexamethylenamin the patient had pain on micturition and slight hematuria.

In May, 1915, the administration of potassium citrate in dosage of 45 grains daily was begun and thenceforth continued at weekly intervals, alternately with the hexamethylenamin. The improvement which followed, however, was broken by relapses in June and July.

Physical examination August 8 showed the child to be slightly anemic, but in good musculature, weighing 31 pounds. The tongue was coated and the right tonsil was slightly enlarged. Cardiac examination detected slight impurity of the first sound as heard in the precordial region, but no organic murmur. The abdomen was unduly prominent. In other respects the findings were negative, except for the urinary examination. This revealed the presence of a moderate number of discrete pus cells.

The hexamethylenamin was discontinued and sodium citrate in dosage of 40 grains daily was prescribed in conjunction with culture of Bacillus Bulgaricus and syrup of the iodide of iron. This treatment was continued indefinitely, and three months after its commencement a report was received stating that the patient had had no relapse and was in better condition than at any time since the discovery of the pyelitis. A urine examination November 27, 1915, showed a very faint trace of albumin and a growth of staphylococcus (apparently due to contamination), but no pus or bacilli.

This case is of interest principally because of the existence of a temperature record kept faithfully by the boy's parents and based on observations morning and evening over a period of a year and a half. The report shows that there were seven distinct relapses of the pyelitis, each of which was productive of fever of 102° or higher, during the period of one year.

Significance of Pyelitis in Boys. Information derived from so small a group of similar cases is necessarily meager, especially since the chronicity of urinary infection of the type under discussion precludes the possibility of sufficiently prolonged individual observation in a given case. Certain general facts, however, seem worthy of special emphasis.

The finding of pus in a male child's urine (in the absence of a specific urethral discharge) should invariably suggest infection of the urinary tract by blood or lymph-stream absorption rather than by direct urethral contamination, which has been shown to afford a very inaccurate explanation of the occurrence of pyelitis, even in the female subject. Pyelitis in the male thus calls for the consideration of the possible existence of an intestinal focus or defect contributing to the escape of the colon bacillus from its normal habitat; and furthermore, pyelitis under these conditions should at least suggest the possibility of colon bacillus septicemia.

Of more practical value is the lesson that in cases of obscure fever in boys as well as girls, microscopic examination of the urine

should never be omitted. History of recent grip or enteritis renders the existence of pyelitis only the more probable, because of the frequency with which pyelitis has been shown to follow these diseases.

The cases reviewed demonstrate more particularly the following clinical facts:

1. Simple pyelitis when subacute, although an undoubted menace, may not prevent a child's physical progress or interfere with a fair degree of health. (Cf. Cases I and II.)

2. Nephritis of fatal outcome may, nevertheless, supervene in kidneys previously subject to pyelitis, even while the urine is clear, of low gravity and albumin content, and free from pus. (Cf. Case II.)

3. Enlarged lymph glands, a recurring skin eruption, pronounced nervous manifestations almost meningeal in type, pains in the muscles, stiffness of the joints, and cough may occupy the foreground in this condition, just as similar symptoms may predominate over the intestinal manifestations in typhoid fever. (Cf. Case I.)

4. A leukocytosis of 34,000 with a polynucleosis of 92 per cent., while calling for surgical coöperation, need not relegate colon bacillus pyelitis, in exceptional instances, outside the domain of medical treatment. (Cf. Case I.)

Modes of Treatment. Three principal methods of attacking deeply seated colon bacillus infections of the urinary tract have been recommended: the administration of drugs excreted in the form of urinary antiseptics, the giving of alkali in some form, and the injection of colon bacillus vaccine.

Hexamethylenamin. Of the so-called urinary antiseptics this alone has gained extensive use in pyelitis. This drug, however, has repeatedly been shown to be without inhibitory or bactericidal action except by virtue of its liberation of formaldehyde, a chemical change occurring only in an acid medium. For this reason it is customary to administer acid sodium phosphate separately while the hexamethylenamin is given, in order to render the urine strongly acid. Burnam's test for formaldehyde[14] has been perfected, with a view of determining actually how much is liberated under dosage with various quantities of hexamethylenamin, and a number of investigators have studied the bactericidal effects of the formaldehyde thus excreted.

Levy and Strauss[15] came to the following conclusions: "Hexamethylenamin *per se* in neutral solutions in concentrations up to 1 to 10 is neither inhibitory nor bactericidal.

Formaldehyde is formed only in the bladder in all cases except

[14] Kaufmann: A Short Method of Testing for Formaldehyde after the Administration of Urotropin, Am. Jour. Obst., lxviii.

[15] A Clinical and Bacteriological Study of Hexamethylenamin as a Urinary Antiseptic, Arch. Int. Med., November, 1914.

in those in which the acidity of the urine is higher than normal. In these cases some formaldehyde is formed in the kidneys.

The strength necessary to inhibit the growth of the colon bacillus is a concentration of 1 to 5000 or greater.

Under a dose of 7 grains three times daily formaldehyde is never present in concentrations greater than 1 to 5000.

The only organism destroyed or inhibited in growth by this concentration is the typhoid bacillus.

For the destruction or inhibition of other organisms a high acidity is necessary and this high acidity in combination with formaldehyde may produce injury of kidney tissue."

Burnam,[16] L'Esperance[17] and Jenness[18] likewise studied the excretion of formaldehyde and found that not over 60 per cent. of all adults are capable of breaking down urotropin even under dosage of 30 to 100 grains; but in conjunction with their findings must be recorded the observations of Talbot and Sisson,[19] who investigated the excretion of urotropin in 44 children and infants and found that although large doses combined with the maintenance of a high degree of acidity of the urine were often necessary, nevertheless all of the children excreted the formaldehyde.

Numerous investigators, moreover, have remarked hematuria (cf. Cases I and III) under what was considered therapeutic dosage.

Before passing final judgment on this mode of treatment, however, the clinician must give due attention to such experience as that of Freeman.[20] He gave as much as 45 grains of hexamethylenamin daily to a child of one year, 35 grains to an infant of nine months, and 25 grains to one of six months, with curative effects, notwithstanding the fact that in every instance other treatment had been employed without avail.

Alkaline Therapy. It has been shown that the ingestion of colon bacilli by leukocytes is most active in an alkaline medium,[21] and this fact, coupled with recognition of the predilection of Bacillus coli for acid media gives ground to the tenet that an alkaline reaction is favorable to the subsidence of pyelitis. Accordingly, advocates of treatment based on this theory have emphasized the need of administering potassium or sodium citrate or a similar salt in dosage sufficiently large and frequent not only to produce but con-

[16] An Experimental Investigation of the Value of Hexamethylenamin and Allied Compounds, Arch. Int. Med., October, 1912, p. 324.

[17] Boston Med. and Surg. Jour., October 24, 1912.

[18] Burnam's Test for Formaldehyde in the Urine: A Study of Two Hundred Cases, Jour. Am. Med. Assn., March 1, 1913, p. 662.

[19] Some Factors Which Influence the Excretion of Formalin in the Urine of Children and Infants Taking Urotropin, Boston Med. and Surg. Jour., April 3, 1913.

[20] The Diagnosis and Treatment of Pyelitis in Infancy, Am. Jour. Dis. Child., August, 1913.

[21] Dick: British Med. Jour., 1910, ii, 1129.

stantly to maintain alkalinity of the urine. Still[22] emphasizes the importance of administering this treatment without interruption at intervals not to exceed three hours even during the time allotted to sleep. In obstinate cases he prescribes also salol. Such beverages as Vichy and lemonade are of obvious value, and the influence of the diet upon the urine reaction is by no means to be forgotten, preference being given to fruit, milk, and vegetables rather than to meat, eggs, and bread.

Many physicians who admit the possibility of ill effects from hexamethylenamin report good results gained by alternating a course of this drug not exceeding a week, with the administration of the alkali for an equivalent period.

Vaccine. Geraghty[23] reports no improvement attributable to autogenous vaccine in any one of 13 adult cases. Chapin and Pisek[24] state that the results from vaccine treatment are very good in colon bacillus infections, but that it is practically impossible by this means to cause a total disappearance of pus and bacilli. Hugh Cabot[25] has stated that vaccines produce improvement in urinary infections in more than half the cases. These few expressions are respectively typical of many others and serve sufficiently to emphasize the variance of view in this matter. The facility, however, with which the particular strain in a given case may be isolated renders the preparation of autogenous vaccine relatively simple and contributes to the justification for its use in all persistent cases. Initial doses ranging from 10,000,000 to 30,000,000 organisms are recommended, and the rapidity of increase and ultimate limitation of the dosage are to be determined by the behavior of the case. Considerable temperature reactions with constitutional disturbances such as occur after immunizing injections of typhoid vaccine are not regarded as cause for discontinuing this treatment provided large and rapidly increasing doses are avoided.

Kidney Lavage.[26] The possibility of developing a method of ureteral catheterization to such a degree as to permit the installation of antiseptic solutions into the pelvis of the kidney in cases of pyelitis in children rests with the genito-urinary specialist. In the female subject the mechanical difficulties attending such

[22] Common Disorders and Diseases of Childhood, 1912, p. 536.

[23] The Treatment of Chronic Pyelitis, Jour. Am. Med. Assn., December 19, 1914, p. 2211. Tr. Am. Assn., Genito-urinary Surgeons, 1910, v.

[24] Diseases of Children, 1915, p. 82.

[25] Am. Jour. Urol., 1911, vii, 131.

[26] Kretschmer, H. L., and Gaarde, F. W.: Treatment of Chronic Colon Bacillus Pyelitis by Pelvic Lavage, Jour. Am. Med. Assn., June 24, 1916, p. 2052. Ayres, W.: Colon Bacillus Infection of the Kidney, New York Med. Rec., May 31, 1913, p. 968. Geraghty: Treatment of Chronic Pyelitis, Jour. Am. Med. Assn., December 19, 1914, p. 2211.

procedure are by no means so great as to discourage trial of this method in expert hands in special instances. Thus far the excellent results obtained from this form of treatment have been practically limited to selected chronic cases in adults.

General Measures. Notwithstanding the fact that there is apparently no reason why absorption and metastasis of bacteria from the intestinal tract may not continue long after the onset of renal infection, few writers emphasize the importance of systematic attack of this primary focus. Colonic irrigations and adequate catharsis are of great value, and of no less value is the maintenance of an easily digestible diet combined with the giving of cultures of Bacillus Bulgaricus or regular doses of salol.

Any of the special methods should always be supplemented by general measures to combat malnutrition and secondary anemia as in the care of tuberculosis. An outdoor life with such play as involves only light exercise does most to ensure against relapses during the period of convalescence.

SUMMARY. Urinary infection caused by the colon bacillus has been shown to be a common and important disease affecting female children. Pyelitis in boys, although far more infrequent, is, from the stand-point of the individual case, possibly even more important.

In the male subject the possibility of extension of infection through the lumen of the urethra may be excluded, and in the treatment of *all* cases the intestine is to be recognized and dealt with as the potential source of the disease.

The possibility of the occurrence of unusual and severe systemic manifestations in well-developed pyelitis should be better appreciated.

The best routine treatment for pyelitis in children is the administration of sufficient alkali to render the urine alkaline and maintain this reaction.

If hexamethylenamin is employed the formaldehyde excretion should be watched and the urine should be examined frequently, with a view of forestalling injurious effects upon the kidney parenchyma.

In all obstinate cases autogenous vaccine should receive a thorough trial.

Courtesies extended by Doctors R. C. Freeman, W. M. Hartshorn, W. Ormiston, and N. N. Forney are herewith gratefully acknowledged.

STUDIES OF THE CEREBROSPINAL FLUID IN ACUTE ANTERIOR POLIOMYELITIS.*

WITH SPECIAL REFERENCE TO THE COLLOIDAL GOLD, POTASSIUM PERMANGANATE REDUCTION, WEIL-KAFKA HEMOLYSIN, AND SAPONIN REACTIONS.†

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The results of the examination of cerebrospinal fluids in acute anterior poliomyelitis summarized in this report are compiled from the routine examinations and special studies‡ of cerebrospinal fluids from patients admitted to the Philadelphia Hospital for Contagious Diseases¶ during the epidemic of the summer of 1916, in an effort to contribute to our knowledge of the changes occurring in the spinal fluid in this disease and the value of its examination as a practical means of diagnosis.

Careful histological studies of the spinal meninges and cords of early experimental and human poliomyelitis infections have shown that the primary reaction of the nervous system is the production of an acute meningitis characterized by hyperemia, edema, and perivascular round-cell infiltration in the pia mater, with subsequent extension into the substance of the cord and involvement of the anterior horn cells. The spinal fluid may be altered by the passage into it of cells from the perivascular and interstitial exudate in the meninges and of serum constituents derived from the hyperemic bloodvessels.

The investigations of Gay and Lucas,[1] and Lucas,[2] confined principally to a study of the cells in the spinal fluids of monkeys experimentally infected and of 11 cases in the preparalytic stage, have shown that the total cell count of the fluid is increased considerably above the normal, the majority of the cells being of the mono-

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‡ Undertaken with the coöperation of Dr. Charles K. Mills and Dr. Allen J. Smith as part of a series of investigations in acute anterior poliomyelitis.

¶ These patients were under the care of Dr. S. S. Woody, chief resident physician, and Dr. Theodore Le Boutillier, Dr. Theodore Weisenberg, Dr. William Drayton and Dr. Maurice Ostheimer of the visiting staff of the hospital.

nuclear variety. Flexner and Lewis[3] in a study of the spinal fluid from a monkey after inoculation with the virus found a considerable increase in the number of cells twenty-four hours after inoculation, and particularly a small cell slightly larger than a lymphocyte showing a polyform nucleus. Sophian[4] reported an increase of globulin in the spinal fluid of cases in the early stages. In a thorough study of 233 fluids from 69 cases, Peabody, Draper and Dochez[5] found an increased cell count, with a low or normal globulin content, in fluids taken during the early days of the disease and before the onset of paralysis; at this time the polymorphonuclear cells amounted to 90 per cent. of the total, although most fluids showed almost exclusively lymphocytes and large mononuclear cells. According to these investigators analogous changes may be found in the spinal fluid of abortive cases; all fluids examined reduced Fehling's solution. They conclude that "the examination of the cerebrospinal fluid in acute poliomyelitis, while giving, as far as is yet known, no specific diagnostic criteria, is of the utmost value as an aid to diagnosis both in preparalytic and in abortive cases." More recent reports of similar findings have been made by Neal and Du Bois[6] and Abramson.[7]

During the recent epidemic of poliomyelitis in Philadelphia we have examined 868 specimens of cerebrospinal fluid from cases of epidemic poliomyelitis admitted to the Philadelphia Hospital for Contagious Diseases and in private practice. In a smaller number of these the histories and clinical studies were sufficiently accurate for purposes of analysis and correlation with the results of laboratory examinations, and the major portion of this laboratory report is based upon these.

1. Physical Properties of the Spinal Fluid in Acute Anterior Poliomyelitis. The majority of the spinal fluids examined by us were water-clear or showed but a faint opalescence when viewed against a black background. Of 316 fluids from cases early in the stage of paralysis, but 5, or from 1 to 2 per cent. of blood-free fluids, were distinctly turbid. Of the fluids of 6 cases which we had the opportunity of examining in the preparalytic stage 2 showed a faint opalescence and 4 were clear. The 5 distinctly turbid fluids were from cases on the fourth, fourth, fifth, sixth, and sixth days after the onset of paralysis, and showed total cell counts of more than 200 cells per cubic millimeter, many of which were polymorphonuclears.

A small fibrin coagulum was noticed in about 10 per cent. of the spinal fluids a few hours after they had been collected and standing in test-tubes. We have not observed xanthochromia or excessive fibrin formation in any specimen.

Many specimens contained small amounts of blood, and while the presence of blood may have been due in certain cases to extravasation from the hyperemia vessels of the pia, we are of the opinion

that in the majority of these fluids, blood gained access by reason of the puncture of vessel with the needle, as only the first flow of fluid contained blood.

2. CYTOLOGY OF THE SPINAL FLUID IN ACUTE ANTERIOR POLIOMYELITIS.* The results of total cell counts with 787 fluids from cases of epidemic poliomyelitis in all stages of the disease are shown in Table I.

TABLE I.—SUMMARY OF RESULTS OF TOTAL CELL COUNTS OF SPINAL FLUIDS IN ACUTE ANTERIOR POLIOMYELITIS.

Cells per cubic millimeter of fluid.				
0 to 12.	13 to 50.	51 to 100.	101 to 500.	Over 500.
178	328	156	95	30

If the upper limit of the normal number of cells per cubic millimeter of cerebrospinal fluid is placed at 12, of these fluids 609, or 77 per cent., showed an increase of cells. In the majority of these the increase of cells was moderate, as 80 per cent. of those fluids containing an increased number of cells the counts were not above 100 cells per cubic millimeter of fluid.

The results of total cell counts in 319 fluids from patients in various stages of epidemic poliomyelitis are classified in Table II according to the day *after the onset of paralysis*. This method of classification was necessary because many cases were not diagnosed or sent to the hospital until paralysis was present, and histories of the preparalytic stage were inaccurate. The cell counts of five cases from private practice in the preparalytic stage are included.

TABLE II.—RESULTS OF TOTAL CELL COUNTS IN VARIOUS STAGES OF POLIOMYELITIS AFTER THE ONSET OF PARALYSIS (319 FLUIDS).

Day of disease.	Total exam.	Cells per cubic millimeter.					Percentage showing increase.
		0–12.	13–50.	51–100.	101–500.	Over 500.	
Preparalytic . . .	5	..	3	2	..	..	100
1 to 3 days . . .	125	19	52	26	24	4	84
4 to 7 " . . .	99	17	51	19	9	3	82
8 to 14 " . . .	55	9	32	8	6	..	83
15 to 21 " . . .	21	8	11	1	1	..	62
22 to 28 " . . .	10	7	2	1	..	..	28
29 to 35 " . . .	4	3	1	..	..	..	25

* In making total cell counts the ordinary leukocyte mixing pipet and the Fuchs-Rosenthal chamber were employed. The diluting fluid which stained the cells and hemolyzed any erythrocytes present was prepared as follows: glacial acetic acid, 1 c.c.; distilled water, 99 c.c.; methyl violet, crystals, 0.1 gm. This fluid was filtered before use. *Counts were made as soon as possible after spinal puncture and only of those fluids showing no macroscopic evidences of blood.* The diluting fluid was drawn into the pipet to the mark 1, the spinal fluid to 11, and the contents mixed by shaking for one minute. After loading the chamber and allowing the cells to settle for five to ten minutes all cells in the ruled-off space were counted and the number multiplied by 11 and divided by 32, which gave the total number of cells per cubic millimeter of fluid.

As shown in Table II an increase of cells was noted in all of the cases examined in the preparalytic stage, and this increase of cells was found in about 95 per cent. of cases to persist for at least three weeks after the onset of paralysis, when the total number of cells gradually approached normal numbers.

The results of differential cell counts with 87 fluids from patients in various stages of the disease after the onset of paralysis are shown in Table III.

TABLE III.—RESULTS OF DIFFERENTIAL CELL COUNTS OF SPINAL FLUIDS IN ACUTE ANTERIOR POLIOMYELITIS AFTER THE ONSET OF PARALYSIS (87 FLUIDS).

Variety of cell.	Under 25 per cent. Cases.	Between 25 to 50 per cent. Cases.	Between 50 to 75 per cent. Cases.	Between 75 to 100 per cent. Cases.
Small lymphocyte	3	3	39	42
Large mononuclears	85	2		
Polymorphonuclears	77	7	1	2
Endothelial	all under 10 per cent.			

As shown in Table III the small lymphocyte variety of cell predominated in the majority of fluids. In over 96 per cent. of these fluids this cell constituted 25 per cent. or more of the cells present.

Cells of the type of large mononuclear leukocytes, while occasionally found, were seldom present in large numbers.

Polymorphonuclear leukocytes predominated in less than 1 per cent. of the fluids examined (3 cases) and in over 88 per cent. constituted less than 25 per cent. of the cells present.

As previously stated the majority of these fluids were from patients in whom paralysis had occurred, whereas the predominance of polymorphonuclear cells is more likely in the preparalytic stage of the disease.

3. Protein Content of the Spinal Fluid in Acute Anterior Poliomyelitis. The routine test for the globulin-albumin content of these spinal fluids was the butyric acid test of Noguchi. Of 868 fluids from patients in various stages of the disease this technic yielded positive reactions with 32 per cent. (Table IV). A comparative study of several similar qualitative methods have shown wide variations in the delicacy of different methods as shown in Table IV.

TABLE IV.—SUMMARY OF RESULTS OF PROTEIN TESTS WITH DIFFERENT METHODS (868 FLUIDS).

Method.	Total exam.	Results. +	Results. −	Percentage positive.
Nonne-Apelt	79	11	68	14
Noguchi	868	280	588	32
Pandy	79	24	55	30
Gordon	79	30	49	37
Kaplan	79	33	46	42

The oldest of these clinical laboratory methods for globulin-albumin in spinal fluid (Nonne-Apelt)* proved the least delicate, and the method of Kaplan, the most delicate. Gordon's method[8] proved quite simple and delicate, while our results with the Pandy test were closely parallel with those of Noguchi's test. The main objections to the latter test and that of Kaplan is the employment of the ill-smelling dilution of butyric acid.

The results of globulin-albumin tests with spinal fluids from patients in various stages of poliomyelitis after the onset of paralysis and employing Noguchi's method is shown in Table V.

TABLE V.—RESULTS OF PROTEIN TESTS (NOGUCHI METHOD) IN VARIOUS STAGES OF ACUTE ANTERIOR POLIOMYELITIS (270 FLUIDS).

Day of disease.	Total exam.	Results. +	Results. −	Percentage positive.
Preparalytic . . .	6	1	5	16
1 to 3 days . .	113	33	80	29
4 to 7 " . .	72	30	42	41
8 to 14 " . .	43	23	20	53
15 to 21 " . .	18	10	8	55
22 to 28 " . .	11	3	8	27
29 to 35 " . .	7	1	6	14

Of the fluids of 6 cases examined in the preparalytic stage but 1 yielded a positive reaction; the percentage of positive reactions then became gradually higher to the third week after the onset of paralysis, when a rapid decrease in positive reactions became

* *Method of Nonne-Apelt.*—This test was conducted by mixing in a small test-tube 1 c.c. of spinal fluid and 1 c.c. of a saturated solution of ammonium sulphate in water; after standing three minutes this tube was compared with a second tube containing cerebrospinal fluid only and an increase of protein was indicated by opalescence, turbidity, and visible precipitation.

Method of Noguchi.—This test was conducted by mixing in a small test-tube 0.2 c.c. of spinal fluid and 1 c.c. of a 10 per cent. solution of butyric acid in physiological salt solution followed by heating to the boiling-point; 0.2 c.c. of normal sodium hydrate was added followed by heating to boiling for a few seconds. Positive reactions were read when marked opalescence or definite floccule formation occurred after standing for an hour. Faint opalescence was regarded as negative.

Method of Pandy.—This test was conducted by mixing in a small test-tube 1 c.c. of a saturated aqueous solution of carbolic acid and one drop spinal fluid. The immediate formation of a definite cloud was regarded as a positive reaction.

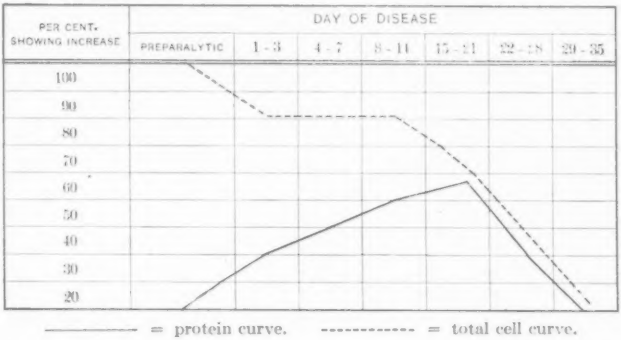
Method of Gordon.[8]—This test was conducted by placing 1 c.c. of spinal fluid in a small test-tube and adding 0.1 c.c. of 1 per cent. solution of bichloride of mercury in distilled water. The development of a cloud or precipitate after standing an hour was regarded as a positive reaction.

Method of Kaplan.—This test was conducted with 0.1, 0.2, 0.3 and 0.4 c.c. of spinal fluid, but the results expressed in Table IV are based upon the reactions observed with 0.2 c.c. of fluid. This amount of fluid was placed in a small test-tube and 0.3 c.c. of distilled water added, followed by heating until the mixture boiled up twice. Three drops of a 5 per cent. solution of butyric acid in physiological salt solution was added and the mixture carefully underlayed with 0.5 c.c. of a saturated aqueous solution of ammonium sulphate. The reactions were read after standing twenty minutes and regarded as positive if a definite ring was apparent; opalescence only was regarded as negative.

apparent. As previously stated, however, and as shown in Chart 1, the cells are increased in the preparalytic and early stages of the disease, the number dropping with the globulin content after the third week following the onset of paralysis.

Accordingly we have found the total cell count alone of most value in aiding the diagnosis of acute anterior poliomyelitis; during the earliest stages of the disease the globulin-albumin tests may or may not be positive, and usually are not. In tuberculosis and meningococcic meningitis, on the other hand, the globulin-albumin tests are usually positive in the early stages, due to the greater degree of involvement of the meninges.

CHART 1.—Curves of total cell and protein increase in cerebrospinal fluid of poliomyelitis.



4. LANGE'S COLLOIDAL GOLD REACTION IN ACUTE ANTERIOR POLIOMYELITIS. While the exact mechanism of the precipitation of colloidal gold and the nature of the substance in cerebrospinal fluid responsible for the phenomenon are unknown it is supposed by many investigators that the precipitating substance is of a protein nature. We have examined the fluids of 38 cases drawn from two to sixteen days after the onset of paralysis with colloidal gold prepared after the method of Miller and his associates,[9] and fulfilling all the requirements of a satisfactory preparation of colloidal gold as emphasized in their paper, to determine if changes occur in poliomyelitis and whether or not these are sufficiently constant to render the test of diagnostic value. The results of these examinations are shown in Chart 2.

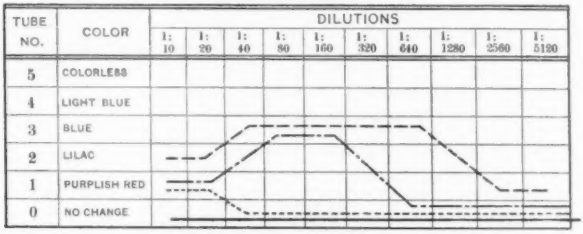
The fluids of 18 cases examined at intervals of two to twelve days after the onset of paralysis showed no color changes at all.

The fluids of 4 cases in the same stages of the disease showed but very slight precipitation in the first two tubes of the series as a 1,100,000,000 reaction. All of these fluids showed an increase of cells and one of them an increase of globulin (Noguchi method).

The fluids of 10 cases examined two to twelve days after the onset of paralysis yielded reactions of the "luetic zone" type with maximum precipitation in the 1 : 40 to 1 : 160 dilutions of fluid with decolorization usually terminating with "blue."

The fluids of 6 cases examined twelve to nineteen days after the onset of paralysis yielded reactions of the "meningitic zone" type characterized by maximum precipitation in dilutions of 1 : 80 to 1:320 or 1:640. All fluids yielded negative Wassermann reactions.

CHART 2.—Summary of results of Lange's colloidal gold reaction with the cerebrospinal fluids of 38 cases of acute anterior poliomyelitis.



———— = observed with the spinal fluids of 18 cases examined 2 to 12 days after the onset of paralysis.

. . . . . = observed with the spinal fluids of 4 cases examined 2 to 12 days after the onset of paralysis.

—.—.—.— = observed with the spinal fluids of 10 cases examined 2 to 12 days after the onset of paralysis ("luetic zone" curve).

— — — — = observed with the spinal fluids of 6 cases examined 12 to 19 days after the onset of paralysis ("meningitic zone" curve).

According to these results, while 40 to 50 per cent. of spinal fluids from cases of epidemic poliomyelitis ranging from the second to the nineteenth day after the onset of paralysis tend to react in a rather constant manner, yielding reactions of the "luetic and meningitic zone" types, similar reactions occur in other forms of meningitis, and we regard the colloidal gold reaction of but helpful diagnostic value; a peculiar or definite curve of precipitation with the spinal fluid of epidemic poliomyelitis did not occur in our experience.

5. MAYERHOFER POTASSIUM PERMANGANATE REDUCTION REACTION IN ACUTE ANTERIOR POLIOMYELITIS. Mayerhofer[10] has proposed the reduction of a decinormal solution of potassium permanganate by 1 c.c. of spinal fluid in an acid medium as an index of the amount of protein substances present and as a method of value in the diagnosis of tuberculous meningitis on the basis that while 1 c.c. of normal spinal fluid usually reduced 2 to 2.3 c.c. of $\frac{N}{10}$ potassium permanganate solution, the fluid of tuberculous meningitis may reduce 3 c.c. or more. Hoffman and Schwartz[11] determined the index on spinal fluids of 3 cases of acute poliomyelitis with readings varying from 2.5 to 3.3 in the acute stage and showing a decline coincident with the disappearance of acute symptoms.

The technic of the test as employed by us is given below.*

We have employed this test in the study of 78 spinal fluids from cases of epidemic poliomyelitis at different stages of the disease ranging from the second to the twenty-first days after the onset of paralysis, with the following reduction indices:

0.7 to 1.1 with the fluids of 6 cases.
1.2 to 1.6 with the fluids of 17 cases.
1.7 to 2.0 with the fluids of 23 cases.
2.4 to 3.6 with the fluids of 31 cases.
6.1 with the fluid of 1 case.

According to Mayerhofer the reduction index may be regarded as increased if over 2.3; the fluids of 32 cases yielded indices over 2.4, indicating that 41 per cent. of the spinal fluids from cases of acute epidemic poliomyelitis in the first three weeks of the infection contain an increased protein content. The determination of the reduction index may be of some practical value in aiding the diagnosis of acute poliomyelitis, as indices of over 2.3 indicate the presence of increased protein due to meningitis.

6. Reduction of Fehling's Solution by Spinal Fluid in Acute Anterior Poliomyelitis. A qualitative Fehling's test† for the presence of dextrose was conducted with 779 spinal fluids from cases of epidemic poliomyelitis in various stages of the disease. Every fluid reduced a portion of the copper solution, but in varying amounts; with 86 fluids the amount of fluid required to effect partial reduction was so large as to indicate that the amount of dextrose was diminished below the normal, but our results in general are in accord with those of previous investigators, indicating that insofar as the qualitative test is concerned there is no constant alteration in the amount of dextrose in the spinal fluid of epidemic poliomyelitis.

7. The Weil-Kafka Hemolysin Reaction in Acute Anterior Poliomyelitis. Normally the blood of over 90 per cent. of persons contains natural antisheep hemolysin, but the cerebrospinal fluid is free of this substance. In meningitis, according to Weil-

* *Technic of the Mayerhofer Reduction Test.*—Place in a beaker 50 c.c. distilled water, 10 c.c. of diluted sulphuric acid (1 part concentrated sulphuric acid and 3 parts distilled water) and 10 c.c. of a decinormal solution of potassium permanganate; boil slowly for ten minutes and determine the amount of decinormal oxalic acid solution required to reduce the potassium permanganate solution until water clear. In a second beaker (thoroughly cleansed) place 1 c.c. of spinal fluid, 50 c.c. distilled water and 10 c.c. of diluted sulphuric acid. Bring to boiling-point, add 10 c.c. decinormal potassium permanganate solution and boil slowly for ten minutes. Turn off the burner and add slowly the amount of decinormal oxalic acid determined in the previous titration. The contents of the beaker turn brown and gradually become water clear. With a burette add decinormal potassium permanganate until the first appearance of a clear rose color. The amount of $\frac{N}{10}$ permanganate solution required represents the "reduction index" of the spinal fluid.

† *Technic.*—0.5 c.c. each of Fehling's alkaline and copper solutions were diluted with 9 parts of water and 1 c.c. brought to boiling-point in a small test-tube; 1 c.c. of spinal fluid was added followed by brief boiling and the occurrence and degree of reduction noted after standing several minutes.

Kafka,[12] the hyperemia and increased permeability of the vessels and exudative processes results in the passage of this hemolysin into the cerebrospinal fluid. Likewise, hemolytic complement is not found in appreciable amounts in normal cerebrospinal fluid, whereas in acute meningitis this substance may be found. Tests of the spinal fluid for natural antisheep hemolysin and complement have been advocated in the diagnosis of meningitis, and particularly in those types caused by Treponema pallidum.

We have employed this test, with certain modifications,* in the study of a number of spinal fluids from normal persons, and cases of anterior poliomyelitis in various stages of the disease for the hemolysin alone and for the hemolysin and hemolytic complement. The results of these tests are summarized in Table VI.

TABLE VI.—SUMMARY OF RESULTS WITH THE WEIL-KAFKA HEMOLYSIN REACTION IN EPIDEMIC POLIOMYELITIS.

Reaction.	Poliomyelitis fluids.			Control fluids.			Per cent. positive in poliomyelitis.
	Total.	+	−	Total	+	−	
For antisheep hemolysin alone	65	43	22	11	0	11	66
For the hemolysin and complement	43	13	30	4	0	4	30

The spinal fluids of 65 cases examined for antisheep hemolysin alone showed the presence of this substance in 43, or 66 per cent., whereas the fluids of 11 control persons were negative. The majority of the fluids containing the hemolysin were from cases of poliomyelitis in the acute stages of the infection.

* 1. Technic for ascertaining the presence of complement and antisheep hemolysin in spinal fluid:

In tube No. 1, 5 c.c. of fresh spinal fluid, free from all traces of blood, were mixed with 1 c.c. of a 2.5 per cent. solution of sheep corpuscles (prepared with physiological salt solution).

In tube No. 2 the spinal fluid was replaced by 5 c.c. of physiological salt solution. This tube served as a control.

The tubes were incubated at 37.5° C. for two hours and centrifugated for a few minutes and the reading of the occurrence and the degree of hemolysis immediately taken. Hemolysis in tube No. 1 indicated the presence of the complement and antisheep hemolysin.

2. Technic for ascertaining the presence of natural antisheep hemolysin alone:

Five cubic centimeter of spinal fluid free from blood and bacterial contamination and 1 c.c. of a 2.5 per cent. sheep corpuscle solution were mixed in a test-tube. A control in which the spinal fluid was replaced by physiological saline solution was also included. The tubes were incubated at 37.5° C. for one hour. They were then centrifuged and the entire supernatant fluid carefully pipetted off. To the sediment of corpuscles 1 c.c. of hemolysin-free guinea-pig complement diluted 1 to 20 with physiological salt solution was added. The tubes were well shaken, reincubated at 37.5° C. for one hour, centrifuged, and the reading of the occurrence and degree of hemolysis taken at once. The occurrence of hemolysis indicated the presence of natural antisheep hemolysin which sensitized the sheep cells followed by hemolysis after the addition of complement. The natural antisheep hemolysin in guinea-pig complement was removed by adding 0.2 c.c. of packed washed sheep corpuscles to 5 c.c. of clear undiluted complement serum. This mixture was kept in a tumbler of cracked ice for one hour, centrifuged, and the clear complement serum used for the dilution.

The spinal fluids of 43 cases examined for hemolytic complement and the hemolysin showed the presence of these substances in 13, or 30 per cent., of fluids from cases in the acute stage of poliomyelitis. The fluids of 4 control cases were found free of both complement and the hemolysin.

The results indicate that in acute anterior poliomyelitis there is present an increased permeability of the vessels with the passage into the cerebrospinal fluid from the blood of both natural anti-sheep hemolysin and complement and particularly the former; a test for these substances may therefore prove of aid in the diagnosis of this infection.

8. Hauptmann's Saponin Reaction in Acute Anterior Poliomyelitis. Solutions of saponin are capable of hemolyzing the erythrocytes of various animals. Hauptmann[13] has found that the cerebrospinal fluid from persons suffering with various diseases of the central nervous system may contain a substance which inhibits this hemolysis. The inhibiting substance is supposed to be cholesterin and the presence of amounts in the spinal fluid sufficient to inhibit saponin hemolysis is regarded as being due to the presence of degenerating lesions with the liberation of cholesterin from the nervous tissues.

We have tested the inhibiting properties of the spinal fluids*

* *Technic of Hauptmann's Saponin Reaction.*—We have modified Hauptmann's original technic and conducted our tests as follows: Nine cubic centimeters of human blood were obtained by venous puncture and mixed with 1 c.c. of a 10 per cent. solution of sodium citrate in physiological salt solution. The blood was then centrifuged and the supernatant fluid withdrawn. The cells were washed three times in physiological salt solution and a 7.5 per cent. suspension in physiological salt solution prepared. The stock solution of saponin was prepared by dissolving 0.5 gram of saponin (Kahlbaum Com.) in 10 c.c. of sterile distilled water. (Solution occurs readily at 37.5° C.). A 1 to 10,000 solution in physiological salt solution was made for each titration from this stock solution. (The stock solution keeps well for one month, after this time the solvent property is greatly delayed.) The titration for dose of saponin was conducted as follows: Into seven test-tubes were placed 0.4, 0.45, 0.5, 0.55, 0.6, 0.65, 0.7 c.c. of the saponin test solution, 0.8 c.c. of physiological salt solution, and 0.5 c.c. of the 7.5 per cent. blood suspension, mixed and incubated at 37.5° C. for one hour. The next dilution of saponin stronger than the one producing complete hemolysis was chosen for the test. The test was then conducted as follows:

Tube 1: 0.8 c.c. clear spinal fluid + determined amount of NaCl + 0.5 c.c. 7.5 per cent. cells.

Tube 2: 0.2 c.c. clear spinal fluid + determined amount of saponin + 0.5 c.c. 7.5 per cent. cells.

Tube 3: 0.4 c.c. clear spinal fluid + determined amount of saponin + 0.5 c.c. 7.5 per cent. cells.

Tube 4: 0.6 c.c. clear spinal fluid + determined amount of saponin + 0.5 c.c. 7.5 per cent. cells.

Tube 5: 0.8 c.c. clear spinal fluid + determined amount of saponin + 0.5 c.c. 7.5 per cent. cells.

Tube 6: 0.8 c.c. NaCl solution + determined amount of saponin + 0.5 c.c. 7.5 per cent. cells.

All tubes were incubated for two hours at 37.5° C. when the reading of the degree of hemolysis was taken, centrifugation being resorted to if necessary.

Tubes No. 1 and 6, being controls, show complete hemolysis; the presence of substances in the spinal fluid inhibiting hemolysis is indicated in the remaining tubes of the series, the degree of inhibition increasing with the larger amounts of spinal fluids.

from 30 cases of acute anterior poliomyelitis during the acute stages of the disease and the fluids of 5 control persons, with negative results in all. Amounts of spinal fluid from the control and poliomyelitis cases ranging from 0.2 to 0.8 c.c. did not produce any appreciable inhibition of hemolysis.

Discussion. The results of these routine examinations and special studies of the spinal fluids from cases of acute poliomyelitis in the recent Philadelphia epidemic have essentially confirmed the findings of Peabody, Draper, Dochez, and other investigators. The greatly desired diagnostic laboratory test for acute anterior poliomyelitis, and particularly in the early stages and for those cases apt to escape clinical detection, has not yet been discovered. None of the physical, chemical, or cytological changes found in the spinal fluid are absolutely confined to acute poliomyelitis or characteristic of this disease; while specific antibodies in the serum have been demonstrated by neutralization of the virus *in vitro* as determined by intracerebral injection into monkeys, this is not a practical diagnostic method and attempts to demonstrate complement-fixing antibodies in the serum and spinal fluid have yielded mostly negative results in the experiments of Gay and Lucas[14] and Kolmer and Freese.[15] Likewise, the microparasite of poliomyelitis discovered by Flexner and Noguchi[16] apparently cannot be cultivated from the cerebrospinal fluid and blood during life, but only from the nervous tissues after death by special methods and under exceptional difficulties, and bacteriological examinations therefor are not available for diagnostic purposes. The easily cultivated streptococci and diplococci found in the brain, cord, and spinal fluid of poliomyelitis, and recently given renewed prominence by the reports of Mathers,[17] Rosenow, Towne and Wheeler,[18] and Nuzum and Herzog[19] do not, in our opinion, possess any diagnostic value; the studies of Kolmer, Brown and Freese[20] with these bacteria are in accord with those investigators who have disregarded these microörganisms as the etiological agent of the disease; we regard these cocci as bearing a relation to poliomyelitis similar to streptococci in scarlet fever. Cultures of the cerebrospinal fluid in acute poliomyelitis during life are sterile in many cases and the presence of an easily cultivated bacterium is always suggestive of contamination. Streptococci are to be found in the tissues of the nervous system and internal organs but only exceptionally in the cerebrospinal fluid during life.

The extent of the changes in the spinal fluid appear to be dependent upon the degree of hyperemia and cellular and serous exudation in the pia mater. As the meningitis produced by the microparasite of poliomyelitis is of an interstitial character rather than a surface infection the alterations of the cerebrospinal fluid from the normal in acute poliomyelitis are not usually as extreme

as found in such infections as those produced by the meningococcus and pneumococcus. For this reason the examination of cerebrospinal fluid must be thorough and employ delicate methods for the detection of abnormal changes. Similar changes in the spinal fluid may occur in tuberculous meningitis, and requires very careful and painstaking search for the tubercle bacillus in the differential diagnosis between the sporadic and atypical case of acute poliomyelitis and tuberculous meningitis. Usually no difficulty is encountered in differentiating from such forms of meningitis as those produced by the meningococcus, pneumococcus, and influenza bacillus on the basis of the high total cell counts, presence of polymorphonuclear leukocytes, large amounts of protein, and the specific microörganism in the cerebrospinal fluid in these infections. The spinal fluid in "serous meningitis," or acute meningeal congestion, may resemble the fluid in acute poliomyelitis insofar that the fluid in both conditions may be clear and under pressure; but the absence of protein increase and an increase of cells in the former usually serve in differentiating between the two conditions.

In acute poliomyelitis a total increase of the cells mostly of the small lymphocyte variety, in a clear or occasionally opalescent spinal fluid under increased pressure, appears to be the earliest and most constant change, while an increase of protein with slight or no alteration in the dextrose content are additional data of value, as are probably also the presence of natural antisheep hemolysin and a substance partially precipitating colloidal gold in dilutions of fluid ranging from 1 : 40 to 1 : 320.

SUMMARY. In the recent epidemic of poliomyelitis in Philadelphia the examination of cerebrospinal fluids yielded the following results:

1. The majority of the fluids were water clear or but faintly opalescent when viewed against a black background; but 1 or 2 per cent. of blood-free fluids presented distinct turbidity. Xanthochromia and excessive fibrin formation were not found; about 10 per cent. of the fluids presented a small fibrin coagulum after standing several hours.

2. Seventy-seven per cent. of the fluids from all stages showed an increase of total cells; in 80 per cent. of these the counts were not above 100 cells per cubic millimeter of fluid. An increase of the total cells was found in the preparalytic stage, and this increase was present in 95 per cent. of cases for at least three weeks after the onset of paralysis, after which the number of cells gradually decreased.

3. In over 96 per cent. of fluids from cases after the onset of paralysis the small lymphocyte variety of cells predominated. Polymorphonuclear cells predominated in less than 1 per cent. of fluids, and in over 88 per cent. constituted less than 25 per cent. of the cells present.

4. An increase of protein was found in 32 to 42 per cent. of fluids, and different tests for protein yielded varying results. With the Noguchi test the fluid of 1 of 6 cases in the preparalytic stage yielded a positive reaction; the percentage of positive reactions then became gradually higher to the third week after the onset of paralysis (55 per cent. positive), when a rapid decrease in protein became apparent.

5. During the acute stages of poliomyelitis the fluids of 40 to 50 per cent. of cases yielded a colloidal gold reaction of the luetic and meningitic zone types. All yielded negative Wassermann reactions. The balance of these fluids produced no precipitation at all, or but slight changes in the 1 : 10 and 1 : 20 dilutions.

6. The potassium permanganate reduction test yielded positive reactions of indices over 2.3, with the spinal fluids of 41 per cent. of cases examined from the second to twenty-first days after the onset of paralysis; a high reduction index indicates an increase of protein in the fluid, and may aid, therefore, in the diagnosis of acute poliomyelitis.

7. Every fluid was found to contain sufficient dextrose to reduce Fehling's solution in some degree; partial reduction of the amount of dextrose was suspected with a number of fluids on the basis of a qualitative test.

8. Increased permeability of the meninges was indicated by the presence of natural antisheep hemolysin in the fluids of 66 per cent. of cases in the acute stages and both the hemolysin and a hemolytic complement in 30 per cent. Both of these substances were absent in the fluids of control persons.

9. Substances inhibiting saponin hemolysis were not found in the fluids of cases two to twenty-one days after the onset of paralysis.

10. A definite and absolute diagnostic criterion or laboratory test with the cerebrospinal fluid in acute anterior poliomyelitis has not been discovered. A clear or slightly opalescent fluid flowing under increased pressure, sterile as examined by smear and culture when collected aseptically, poor in fibrin, reducing Fehling's solution and containing an increased number of cells chiefly of the mononuclear variety, are the most constant findings. An increase of protein and a high potassium permanganate reduction index strengthen the diagnosis, while a colloidal gold reaction of the luetic and meningitic zone types and the presence of natural antisheep hemolysin are helpful diagnostic data.

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POST-TRANSFUSION REACTIONS: A REVIEW OF 280 TRANSFUSIONS PERFORMED IN THE WARDS OF PRESBYTERIAN HOSPITAL, NEW YORK CITY.

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Transfusions can now be performed with such ease and safety that their use has become very popular in a great variety of clinical conditions. In fact, the treatment is probably resorted to in many cases in which it does no good, and perhaps does harm to the patient. It is therefore worth while to determine the conditions in which

transfusions are of benefit, and to eliminate their use from conditions in which they are useless, lest they fall into disrepute by unintelligent use, only to be revived when their real value can be more definitely determined. The febrile reaction which so frequently follows transfusion is an unpleasant phenomenon, the nature of which is as yet very poorly understood, and which is sometimes so severe as to be alarming. The purpose of this review is to discover in which conditions transfusion is a proper therapeutic measure, what the real cause of the post-transfusion reaction is, and what factors in its production can be eliminated.

We have reviewed 280 transfusions performed on 99 different patients, 57 of whom were males, 42 females; 35 were suffering from surgical conditions, 64 from medical conditions. In the surgical cases transfusion was performed in three general types of cases: (1) just before or during operation to prevent shock or counteract excessive hemorrhage, (2) for postoperative hemorrhage, (3) as a last resort in desperately sick patients after operation. Among the medical cases, 40 were suffering from pernicious anemia. These cases comprise the major part of our series, and 164 transfusions, 58 per cent. of the whole series, were performed on them. The other medical cases are in four classes, namely, (1) other blood diseases, such as leukemia, Hodgkin's disease and splenic anemia; (2) secondary anemias, including cases of acute hemorrhage from various causes; (3) cases of bacteriemia.

The question of the therapeutic value of transfusion, and what the indications are for its use, involves the careful study of temporary and permanent effects in the conditions in which it is used. For this there is not space in this review. The cases in which it was used in our series were very largely cases suffering from incurable disease, the treatment being used merely as a palliative measure. This is shown by the final outcome of the cases:

Cured	10 per cent.
Improved	36 "
Unimproved	6 "
Died	48 "

This, however, does not detract from the value of transfusion, for many cases of incurable disease, such as pernicious anemia, have been given months of fairly good health, and in many cases spontaneous remissions have been definitely hastened. The cured cases in our series were, with one exception, clean operative cases transfused just before, during, or after operation. The other cured case was one of typhoid fever with intestinal hemorrhage. The cases discharged "improved" include many cases of pernicious anemia and cases of hematemesis or other forms of acute hemorrhage in which transfusion seems to be of distinct advantage. The unimproved cases and those which died include incurable primary

blood disease and cases of sepsis and bacteriemia. These latter, whether surgical cases with undiscovered foci of suppuration, or medical cases of bacteriemia, benefited least by transfusion, not a single case having recovered. The other condition in our series which seems distinctly not to have been helped even temporarily is acute leukemia.

METHODS OF TRANSFUSION. The methods of transfusion used ir this series were as follows:

Sodium citrate method	196	transfusions,	70.0 per cent.
Syringe cannula method (Lindemann)	73	"	26.4 "
Defibrination method	5	"	1.8 "
Washed blood cells	3	"	1.0 "
Arteriovenous suture	2	"	0.8 "
Hirudin method	1	"	0.4 "

In the sodium citrate method, perfected by Lewisohn,[1] the blood was taken through a large needle from a vein at the donor's elbow into a flask containing sodium citrate solution. In no case was it necessary to cut down on the donor's vein. 5, 8 or 10 per cent. sodium citrate solution was used, made up from chemically pure sodium citrate crystals dissolved in freshly distilled water and sterilized in an autoclave. The final dilution of sodium citrate averaged 0.5 per cent. Although blood can usually be kept from clotting by a 0.2 per cent. solution, it has occasionally clotted with that dilution during administration, and since toxic symptoms were not observed in our series from as much as 5 gms. of the drug, which is equivalent to 0.5 per cent. in 1000 c.c. of blood, the latter dilution has been considered better. After collecting the blood it is strained through sterile gauze into a second flask to remove any small clots, and is administered by drawing it through glass tubing jointed with short rubber tubes, through a 3-way stop-cock into a glass syringe, and is thence injected through the stop-cock and a medium-sized needle into the recipient's vein. This syringe method of administration is used because it is frequently difficult to enter and stay in the recipient's vein with a needle large enough to let the blood flow by gravity, and it is quicker and neater, and preserves the recipient's vein better, to avoid cutting down on the vein by using the small needle. All the apparatus is sterilized in water distilled the day it is used, except the flasks and needles, which are dry sterilized. The apparatus is flushed out with citrate solution before the blood enters it, in order to prevent slight hemolysis from the water in the tubing. By this method a complete transfusion of 500 c.c. of blood can be performed by one person in about thirty minutes. It is the method which is used as a routine at the Presbyterian Hospital at the present time.

In 3 cases it was impossible to secure a donor belonging to the same blood group as the patient. A donor was therefore secured from a blood group whose cells would not be agglutinated by the

patient's serum, but whose serum would agglutinate the patient's blood cells. The blood was taken in citrate solution, centrifuged, the serum removed, and the cells washed once and suspended in an equal volume of normal saline prepared from freshly distilled water. The cell suspension was then administered to the patient in the usual way, and no untoward effect was noted in any case. Minot[2] states that no untoward symptoms occur in transfusions in which donor and recipient belong to different groups so long as the donor's cells will not be agglutinated by the recipient's serum, even though the donor's serum will agglutinate the recipient's cells. The apparent cause is the dilution of the donor's serum by that of the recipient. This was not done in any cases in our series.

The transfusions performed by means of hirudin to prevent plotting and by arteriovenous suture are included as examples of methods not now in common use.

Blood Grouping. The grouping of donor's with recipient's blood to assure the absence of agglutinins and hemolysins in one blood for the other was carried out in almost every case. In 5 cases in the early days of the syringe cannula method there is no record that it was done. In one other case, No. 7, there is a statement that it was not done. In this case, one of prolonged uterine hemorrhage, 300 c.c. of blood was taken from each of two daughters by the syringe cannula method. Immediately afterward the patient complained of air hunger and pain and oppression in the chest, which was unrelieved by medication, and eight hours later she suddenly went into collapse and died. The case is considered one in which the blood of the recipient was incompatible with that of one or both donors, although no examination of the blood or urine of the recipient was made after the transfusion.

In all except the above 6 cases, donor's and recipient's blood were either tested directly against each other or were grouped according to the method of Epstein and Ottenberg.[3] Table I shows the agglutination and hemolysis reactions which are the basis of this grouping, the plus sign standing for hemolysis and agglutination of the cells by the corresponding serum.

TABLE I.

	Group.	Serum. I.	II.	III.	IV.
Cells	I	0	0	0	0
	II	+	0	+	0
	III	+	+	0	0
	IV	+	+	+	0

Group I may be called the strongest group, its cells not being agglutinated or hemolyzed by the serum of any other group, and its serum containing agglutinins and hemolysins for the cells of all the other groups. Group IV, on the other hand, is the weakest group, its cells being agglutinated and hemolyzed by the serum of

all the other groups, and its serum not containing agglutinins or hemolysins for any human blood.

The technic now followed in our laboratory by Miss Miriam Olmstead for the grouping of blood is that devised by Epstein and Ottenberg,[4] and is as follows: Samples of serum and cells of known group are kept ready for use. Two specimens of blood are taken from the person to be grouped, one in a dry test-tube and one in normal saline. The former is allowed to clot and is centrifuged to separate the serum. The blood taken in saline is centrifuged, the saline pipetted off, the cells washed and a 5 per cent. suspension in saline prepared. A drop of the cell suspension is mixed in a capillary pipet with a drop of the serum from known groups and the pipet sealed. The same thing is done with a drop of the unknown serum with known cells. The tubes are then incubated at 37° C. for twenty minutes, at which time they can usually be safely read. Agglutination, if present, can be detected macroscopically, the cells gathering into long strings. Hemolysis is sometimes also evident, but as agglutination is always present in incompatible bloods, whether or not there is hemolysis, the latter need not be ascertained. The pipets are then left at room temperature for two hours before the final reading is made, and in case two bloods are being matched directly and no agglutination is evident at the end of two hours, a final reading is not made until the following day.

Specimens of blood belonging to Group III are occasionally met with, Miss Olmstead tells us, whose serum has no agglutinins for Group II. The final test for these specimens, to distinguish them from Group IV, which also has no agglutinins for Group II, must be their ability to agglutinate the cells of Group IV and the inability of the serum of Group III to agglutinate their cells. As Group IV blood is usually not available, the latter point must usually be the deciding one.

It is really necessary, as Moss[5] has shown, to use only the cells of Groups II and III against the serum of the blood to be grouped, or the serum of Groups II and III against the cells of the blood to be grouped, as the cells or serum from each of the four groups will act differently toward the serum or cells of these two groups. As serum can be preserved much better than cells, the serums of Groups II and III are the most valuable specimens to have on hand. For purposes of control, however, it is wise to use blood from all three of the common groups if they are available.

A more rapid method of grouping which we use in emergency cases, and which has proved just as reliable as that given above, is as follows: The cells and serum are prepared as described above. A drop of cell suspension and serum for each test are then mixed together on one end of a glass slide, and are let stand at room temperature for five minutes. A small drop of the mixture is then

diluted with a drop of saline at the other end of the slide, and a cover-slip applied. Any agglutination is evident at once microscopically, the cells gathering together in bunches of irregular shape. The appearance is distinctly different from rouleaux formation where the cells are in chains and overlap each other regularly. Ten minutes later the agglutination is evident macroscopically in the original mixture at the other end of the slide.

Before the introduction of the classification into blood groups, donor and recipient were grouped directly in every case, but for the last two years, which covers the period of practically all the transfusions by the citrate method in this series, most of the cases have been grouped from stock specimens of known blood, and transfused from a donor whose group had been previously determined, without testing donor's and recipient's blood directly. In this way emergency transfusions have been performed on very short notice, and in no case has there been any evidence of incompatibility. In several cases blood for grouping has been taken from the donor at the time of transfusion, and donor and recipient tested directly to check up results. In no case has any incompatibility been found. Nor have the post-transfusion reactions been any more numerous during the period of the citrate transfusions, as will be shown later in Table IV. It must be said, however, that unless a reliable laboratory is at hand to carry out such a system of grouping, the direct test of the donor's blood against the recipient's is the only way to be sure of their compatibility.

Of the 67 patients in this series whose blood group was determined, the groups were represented as follows:

Group I	31 cases, or 46 per cent.
Group II	26 cases, or 39 "
Group III	9 cases, or 13 "
Group IV	1 case, or 2 "

Groups I and II are therefore much the commonest groups.

Post-transfusion Reactions. The post-transfusion reaction is an occurrence which has been met with by all who have used the treatment, no matter what method of transfusion is employed. The typical reaction consists of a chill, coming on about one-half hour after the transfusion, a sharp rise of temperature, gradually subsiding to normal in three to eight hours, sometimes nausea, vomiting, pains in various parts of the body, and skin eruptions, especially urticaria and localized areas of edema. There is great variation in the degree of reaction, from a slight rise of temperature with no other symptoms, to a rise of temperature to 105° with all the other symptoms mentioned above.

In classifying our transfusions according to the degree of reaction, the rise of temperature alone has been considered. So many patients have a normal rectal temperature of 99° F. that unless

there was a rise to 100° or over the patient was classified as having no reaction. Table II shows the percentage of reactions of various degrees:

TABLE II.

Degree of reaction.	Highest temp. Fahr.	Number of transfusions.	Percentage of transfusions.
0	99.8°	102	36.4
1	100° to 101.8°	60	21.4
2	102° to 103.8°	76	27.2
3	104°+	42	15.0

It will be seen that 36.4 per cent. of the transfusions were not followed by any reaction, 63.6 per cent. were followed by some degree of reaction. These figures are therefore the control figures for the examination of the factors which may cause the reaction. These factors will now be considered.

I. *The Relation of the Recipient's General Condition to the Reaction.* Table III shows the relative number of reactions among recipients who were in good, fair, and poor condition at the time of transfusion:

TABLE III.

Condition.	Number of transfusions.	Number of reactions.	Percentage of reactions.
Good	167	134	74
Fair	68	35	51
Poor	45	19	42

This factor is, of course, a negative rather than a positive one, for the good condition of the patient cannot be said to be a cause for the reaction. Poor condition is rather a cause for the absence of it. Nevertheless it is evident that the reaction is dependent to a considerable degree upon the ability of the body to respond to the introduction of a foreign substance.

II. *The Relation of the Method of Administration to the Reaction.* Table IV shows the comparative number of reactions following transfusions by the citrate and syringe cannula methods. The number of transfusions by the other methods in our series is too small for comparison.

TABLE IV.

Method.	Number of transfusions.	Number of reactions.	Percentage of reactions.
Citrate	196	127	64.8
Syringe cannula	73	47	64.4

The reaction following one of the transfusions by the syringe cannula method was undoubtedly a so-called "water reaction," the reaction first explained by Wechselmann[6] in connection with intravenous salvarsan administration, and shown to be due to a

fungous growth in supposedly sterile, distilled water after it has stood for several days. In this case, No. 63, donor and recipient both received normal saline intravenously, as is frequently necessary in the syringe cannula method. The saline had been prepared from water distilled several days before. Immediately after the transfusion both donor and recipient experienced a severe chill, with a rise of temperature to 103°, nausea and vomiting. Their temperatures did not reach normal until three days after the transfusion. Since then only water distilled on the day of the transfusion has been used either for administration to the patient as saline or citrate solution intravenously, or in the preparation of the apparatus. Although some of the transfusions by the syringe cannula method preceding this one may have been followed by a water reaction, it is probably a negligible factor in the total percentage of reactions, since in subsequent transfusions by the syringe cannula method, when only freshly distilled water was used, 67 per cent. of the cases still had reactions. It is therefore evident that the method of transfusion has nothing to do with the production of a reaction.

III. *The Relation of Blood Relationship to the Reaction.* Table V shows the relative frequency of reactions in cases where donor and recipient were or were not blood relations.

TABLE V.

Blood relationship.	Number of transfusions.	Number of reactions.	Percentage of reactions.
Yes	40	24	60
No	236	155	66
Not recorded	4		

With such a comparatively small number of blood relations in the series, this difference of 6 per cent. is negligible, and it is evident that, so far as liability to reaction is concerned, blood relationship is of no advantage in procuring the best possible donor for a patient.

IV. *The Relation of Blood Groups to the Reaction.* Table VI shows the relative number of reactions in the different blood groups.

TABLE VI.

Blood group.	Number of transfusions.	Number of reactions.	Percentage of reactions
I	123	83	68
II	68	44	65
III	36	24	66
IV	1	1	100
Not recorded	52		

In the three common groups, and probably in Group IV also, there is practically no difference in the relative compatibility of

the blood of individuals within each group. The factor of incompatibility which is responsible for reactions in cases which have been properly grouped is therefore something which is not detected by the ordinary method of testing for agglutination and hemolysis.

V. *The Relation of the Amount of Blood Given to the Reaction.* Table VII shows the relative frequency of reactions following transfusions of large and small amounts of blood.

TABLE VII.

Amount of blood.	Number of transfusions.	Number of reactions.	Percentage of reactions.
Less than 200 c.c.	11	1	9
More than 200 c.c.	260	175	67
Not recorded	9		

Among the transfusions of more than 200 c.c. the percentage of reactions from transfusions of 300 c.c., 400 c.c., 500 c.c., etc., is fairly uniform, which warrants their being grouped together. Although the number of transfusions of less than 200 c.c. is too small to be very conclusive, nevertheless the contrast in the percentage of reactions is very striking, and it is possible that reactions could be practically eliminated if amounts of 200 c.c. or less were given frequently, rather than larger amounts at greater intervals.

VI. *The Relation of Subsequent Transfusions to the Reaction.* This refers to all transfusions administered to one patient from any donor. The greatest number of transfusions given to one patient in this series was 23, which were donated to a case of pernicious anemia. Five different donors were used, one as many as nine times. Table VIII shows the increase of reactions in subsequent transfusions.

TABLE VIII.

No. of the transfusion.	Number of transfusions.	Number of reactions.	Percentage of reactions.
1st	99	60	60
2d	53	31	59
3d	33	22	67
4th	25	17	68
Over 4th	70	52	74

At first the increase in percentage of reactions with subsequent transfusions does not appear striking, but when it is remembered that the patients who receive the larger number of transfusions are usually those whose condition ultimately becomes poorer, and their power of reaction therefore less, the figures are more conclusive. It would seem, therefore, that there is a tendency for an increase in the liability to reaction with subsequent transfusions.

VII. *The Relation of Subsequent Donation to the Reaction.* This refers to the number of times the same donor was used for a single recipient. The largest number of donations in this series by a single donor to a single recipient was 9, the case mentioned above. Table IX shows the increase in reactions with subsequent donations.

TABLE IX.

Number of the transfusion.	Number of transfusions.	Number of reactions.	Percentage of reactions.
1st	184	105	57
2d	40	28	70
3d	22	16	73
4th	11	10	91

Beyond the fourth donations the figures are too small for a fair comparison. It is evident from this table that subsequent donation tends to increase the frequency of reaction. The tendency to post-transfusion reaction may therefore be lessened by using different donors in cases which need many transfusions.

VIII. *The Tendency for Individual Donors to Cause Reactions.* Of the 108 donors used in this series, 6 were used twelve or more times, and therefore offer enough statistics from which to draw conclusions as to their tendency to cause reactions. This is shown in Table X.

TABLE X.

Donor.	Number of transfusions.	Number of reactions.	Percentage of reactions.
J. K.	36	28	78
H. T.	16	14	88
C. J.	16	12	75
E. D.	15	11	73
C. C.	15	7	47
A. A.	12	6	50

Fifty per cent. of J. K.'s donations and 62 per cent. of H. T.'s were followed by reactions with a temperature of 102° or over. These are in contrast to the last two, C. C. and A. A., only 33 per cent. of their donations being accompanied by a temperature of 102° or over. There is therefore considerable difference between donors in their tendency to cause reactions.

Post-transfusion Leukocytosis. The similarity of some of the post-transfusion reactions to those caused by the intravenous administration of typhoid vaccine,[7] in which there was a marked transient polymorphonuclear leukocytosis, led us to follow closely the white blood cells in a few cases during their post-transfusion reactions.

Case 224.—Pernicious anemia: In good condition, was given 600 c.c. of blood by the citrate method. Blood count before transfusion showed red blood cells 1,066,000, hemoglobin 45 per

cent. The next day red blood cells 1,760,000, hemoglobin 53 per cent. Transfusion was followed by a chill and temperature of 104.2°. White blood cells changed as follows:

Before transfusion, white blood cells	5,300,	polynuclears	59	per cent.
Three hours after transfusion, white blood cells	8,500,	"	83	"
Seven hours after transfusion, white blood cells	11,600,	"	80	"
Fifteen hours after transfusion, white blood cells	27,000			
Seventeen hours after transfusion, white blood cells	19,500,	"	81	"
Nineteen hours after transfusion, white blood cells	15,600			
Twenty-three hours after transfusion, white blood cells	13,800,	"	82	"
Twenty-seven hours after transfusion, white blood cells	9,700,	"	81	"

One week later red blood cells were 1,800,000, hemoglobin 64 per cent., and the patient was discharged much improved after a second transfusion a week later, with red blood cells 2,100,000, hemoglobin 66 per cent. This was evidently a case in which spontaneous remission was possible.

CASE 270.—Diabetes and metrorrhagia: In good condition; was given 500 c.c. of blood by the citrate method. Before transfusion red blood cells 3,300,000, hemoglobin 30 per cent. Ten days after transfusion red blood cells 4,600,000, hemoglobin 55 per cent. Transfusion was followed by a chill lasting twenty-five minutes, with nausea and vomiting and a rise of temperature to 103.8°, falling gradually to 99.4° twenty-three hours after transfusion. The white blood cells changed as follows:

Before transfusion, white blood cells	5,400,	polynuclears	54	per cent.
One-quarter hour after transfusion, white blood cells	6,100,	"	70	"
Two hours after transfusion, white blood cells	6,300			
Five hours after transfusion, white blood cells	14,300,	"	91	"
Seventeen hours after transfusion, white blood cells	9,000,	"	85	"
Twenty-four hours after transfusion, white blood cells	5,300,	"	82	"
Twenty-nine hours after transfusion, white blood cells	5,200,	"	88	"

Dilatation and curettage was performed six weeks after transfusion and patient was discharged, with red blood cells 4,460,000 and general condition greatly improved.

CASE 185.—Pernicious anemia: In good condition; was given 275 c.c. of blood by the citrate method. Before transfusion red blood cells were 920,000, hemoglobin 36 per cent. Twenty-four hours after transfusion red blood cells 900,000. One week later red blood cells 1,030,000, hemoglobin 25 per cent. Transfusion was followed by a chill lasting twenty minutes, and temperature

reached 105° five hours later and then fell rapidly to 100° seven hours after transfusion. White blood cells changed as follows:

Before transfusion, white blood cells	5,200, polynuclears 62 per cent.
One-quarter hour after transfusion, white blood cells	5,870
Three hours after transfusion, white blood cells	4,150
Six hours after transfusion, white blood cells	4,000
Fourteen hours after transfusion, white blood cells	4,800

This patient was in the hospital two and a half months and received five transfusions, but his red blood cells never exceeded 2,300,000. He was apparently a case without the power of spontaneous remission.

CASE 230.—Pernicious anemia: In good condition; was given 350 c.c. of blood by the citrate method. Before transfusion red blood cells were 850,000, hemoglobin 30 per cent. Twenty-four hours after transfusion red blood cells 1,660,000, hemoglobin 33 per cent. Three days later red blood cells 1,490,000, hemoglobin 33 per cent. Three weeks later red blood cells had again fallen to 826,000, hemoglobin 20 per cent. Following transfusion the patient had a chill and the temperature rose to 103.6° two hours later, falling gradually to 98.6° twenty hours after transfusion. White blood cells changed as follows:

Before transfusion, white blood cells	2,800, polynuclears 34 per cent.
Two hours after transfusion, white blood cells	1,400
Three hours after transfusion, white blood cells	1,200
Six hours after transfusion, white blood cells	1,800
Sixteen hours after transfusion, white blood cells	2,800
Twenty-eight hours after transfusion, white blood cells	2,800

This patient had nine transfusions, but his red blood cells never exceeded 2,200,000, and he died two and a half months after his first transfusion. He was another case without the power of spontaneous remission.

The absence of leukocytosis in the last 2 cases is in accordance with the failure of their blood to recuperate when stimulated by transfusion. In the same type of case an absence of leukocytosis is also seen in the presence of acute infection. In fact, Case 185, after a subsequent transfusion, developed facial erysipelas, and during the course of that infection his white blood cells never rose above 9100, with 65 per cent. polymorphonuclear leukocytes. A further study of the white blood cells during post-transfusion reactions in cases other than pernicious anemia, might show a constant occurrence of leukocytosis similar to that following the intravenous administration of a foreign protein.

DISCUSSION OF REACTIONS. There are several possibilities as to the main cause of the post-transfusion reaction. These possibilities are: (1) The water used in preparation of the apparatus or

in the saline or citrate solutions; (2) impurities in sodium chloride or sodium citrate used; (3) hemolysis or agglutination of red blood cells; (4) trauma to the red blood cells by manipulation, with resultant hemolysis; (5) a change in the plasma protein by its contact with a foreign substance; (6) the interaction of plasma ferments with the partial splitting of the foreign protein introduced; (7) the presence of antibodies in the recipient's blood which split up the foreign protein introduced. These will now be considered one at a time.

1. Water distilled on the day it is used has been shown to be uniformly incapable of causing febrile reactions and can therefore be eliminated as a factor.

2. The use of chemically pure salts should free them from suspicion as factors in causing a reaction. Moreover, one would expect more uniformity in the occurrence of the reaction if the salts were a factor. That the amount of sodium citrate administered had nothing to do with the occurrence of the reaction is shown by Table XI, which shows the amount of citrate and the corresponding reactions in the 119 cases where the amount given is stated in our records.

TABLE XI.

Grams of citrate.	Number of cases of no reaction.	Number of cases of first-degree reaction.	Number of cases of second-degree reaction.	Number of cases of third-degree reaction.
0 to 1	1	4	2	4
1 to 2	11	6	8	4
2 to 3	25	10	23	8
3 to 4	4	2	4	2
4 to 5	0	0	0	0
5 to 6	1	0	0	0

The case receiving the largest amount of citrate had no reaction. Furthermore, the occurrence of as high a percentage of reactions by the syringe cannula method as by the citrate method eliminates this factor.

3. Lindemann[8] ascribes the reaction solely to the intravascular occurrence of hemolysis, comparing it to the chill and fever in malaria at the time of the bursting of the red blood cells, liberating the organism, and he states that very careful grouping of donor and recipient can eliminate hemolysis. In his series of 155 transfusions, in which he personally supervised the selection of donors in all except 9 cases, there occurred 21 cases of a rise of temperature of 2° or over which are not explained unless hemolysis occurred *in vivo* but not *in vitro*. This, of course, is possible, and if so, would be impossible to eliminate.

Brown[9] showed that the malaria pigment liberated at the time of the bursting of the red blood cells is hematin. By injecting this substance into animals[10] he produced a febrile paroxysm similar to the malarial paroxysm.

It is well known that in paroxysmal hemoglobinuria the attacks are accompanied by a chill and febrile reaction very similar to that following transfusion. Hoover and Stone,[11] in a study of 2 cases of this disease, found a marked polymorphonuclear leukocytosis accompanying the attacks, which is similar to that we have shown above with post-transfusion reactions. They also claim that the only blood pigment found in the blood plasma at the time of the attack is oxyhemoglobin.

The examination of the urine to detect the presence of marked blood destruction *in vivo* might be expected to throw some light on the relation of blood destruction to the post-transfusion reaction. In malaria the paroxysm is followed by an abundance of urobilin in the urine. In paroxysmal hemoglobinuria the disease takes its name from the excretion of large amounts of hemoglobin in the urine. In our series of transfusions, however, the relation of the reaction to the excretion of urobilin and hemoglobin is by no means definite. Table XII shows this relation in cases in which the urine was examined after transfusion.

TABLE XII.

	Number of cases of			
	No reaction.	First-degree reaction.	Second-degree reaction	Third-degree reaction.
Urobilin absent	18	19	32	11
present	5	9	5	2
Hemoglobin absent	27	25	36	16
present	3	2	7	3

It will be seen that in cases of even severe reaction, both urobilin and hemoglobin were absent in the large majority of cases after transfusion. Furthermore, as urinary tests for these substances were not made before transfusion, urobilin may have been present in some cases before as well as after transfusion, as it frequently is in pernicious anemia. This source of evidence of blood destruction as the cause of the post-transfusion reaction therefore seems very small. Hemolysis cannot, however, be disregarded as the possible cause of some of the reactions.

The occurrence of a slight amount of agglutination of transfused cells after proper grouping of donor and recipient is also a possibility, the presence of which would be very difficult to determine. A very careful examination of the recipient's blood during the reaction would be necessary, which was not done in any case in our series.

4. Trauma to the red blood cells by manipulation during the transfusion may be excluded as a possible cause of the reaction, since the amount of trauma is practically uniform in all transfusions by a single method, while the occurrence of the reaction is far from uniform. Moreover, in the cases in our series where defibrinated blood was used, in which method there is undoubtedly more trauma to the red blood cells than by the other methods, no reactions occurred.

5. The change of plasma protein by its contact with glassware, metal and rubber tubing can also be eliminated because of the lack of uniformity of the occurrence of the reactions, under similar methods of treating the blood.

6. The production of the reaction by the partial splitting of the foreign protein introduced, with the formation of a toxic product, either by the interaction of plasma ferments or by the presence or acquisition of antibodies in the recipient's blood, takes us into a field which has as yet been but slightly investigated. There are several points in our findings, however, that suggest that the post-transfusion reaction may be one of this type. The reaction in most cases is, of course, much less severe than the typical foreign protein reaction, but as the protein introduced is only slightly, if at all, different from the recipient's plasma, a reaction of extreme grade would not be expected. The absence of a reaction with small amounts of blood, the progressive increase of reaction with subsequent transfusions, and especially with subsequent donations by the same donor, the tendency of some donors to cause more reactions than others, and the occasional occurrence of transient polymorphonuclear leukocytosis, all tend to support this view. No more definite conclusions can be drawn on this point until the subject has received much more detailed study.

CONCLUSIONS. 1. Transfusion is of real value in cases of hemorrhage, in clean operative cases, in pernicious anemia, and in some secondary anemias. It is of little or no value in septic operative cases, cases of bacteriemia, or cases of acute leukemia.

2. The sodium citrate method of transfusion is a very simple and satisfactory method. A dilution of citrate up to 0.5 per cent in 1000 c.c. of blood can be used without producing toxic symptoms in an adult, and that dilution prevents clotting better than a dilution of 0.2 per cent.

3. Blood grouping should always be carried out before a transfusion. Where a reliable laboratory is at hand the direct grouping of donor and recipient is not necessary, but otherwise should always be performed. Failure to determine the compatibility of the bloods may result in the sudden death of the patient.

4. Post-transfusion reactions occurred in 63.6 per cent. of the cases in our series, the reactions varying greatly in degree, but all being evidenced by a rise of temperature to 100° or more.

5. The recipient in good general condition is much more likely to have a reaction than the one in poor condition.

6. The method of transfusion, the blood relationship of donor and recipient, and the blood group of the recipient seem to have nothing to do with the occurrence of the reaction.

7. Transfusions of small amounts of blood, *i. e.*, less than 200 c.c., are less likely to be followed by reactions than are transfusions of larger amounts.

8. The more transfusions a patient is given the more likely he is to have a reaction, especially if the same donor is used a large number of times. The blood of some donors is more likely to cause reactions than the blood of others.

9. In some cases the post-transfusion reaction is accompanied by a marked polymorphonuclear leukocytosis. Whether this is due to intravascular hemolysis or to the formation of a toxic product from the partial splitting of a foreign protein cannot at present be stated. It seems most likely, however, that one of these phenomena is probably responsible for most post-transfusion reactions.

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MENINGITIS SYMPATHICA.[1]

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Meningitis sympathica, so named by Plaut and Schottmüller,[2] is a condition of the cerebrospinal fluid caused by inflammation in the neighborhood of the meninges: (1) It is characterized by an increase in the pressure of the fluid, which sometimes registers as high as 400 mm. in the Strauss[3] lumbar-puncture instrument. (2) There is generally a considerable or moderate increase of the albumin content and cellular elements. The cells are usually polymorphonuclear leukocytes, but occasionally they are lymphocytes. (3) The fluid, which may be clear or turbid, is sterile. (4) There may be symptoms of meningitis.

[1] A part of the subject matter of this paper was read at the meeting of the American Association of Neurologists in New York.
[2] Leitfaden zur Untersuchung der Zerebrospinalflussigkeit.
[3] Jour. Am. Med. Assn., lxii, 1327.

Brain abscess is one of the most frequent causes of meningitis sympathica, and the latter condition may be of great assistance in the diagnosis of the former. This is especially true of cases in which there has been a previous otitic inflammation with or without mastoid or lateral sinus involvement. The following case is an illustration:

CASE I.—A. F., admitted to the service of Dr. Whiting, December 1, 1912, with the diagnosis of mastoiditis. The following day 12 c.c. of cloudy spinal fluid under increased pressure was removed. This fluid showed an increase in albumin content and an increased number of leukocytes and sugar reduction. Cell count: polymorphonuclear, 91 per cent.; mononuclear, 9 per cent. Fluid sterile. Operation for mastoiditis. Lateral sinus exposed and found clear. The dura opened, but no meningitis was discovered. Subsequently, rigidity of the neck and marked Kernig developed. Blood cultures were found sterile; the jugular was exposed and tied. At the same time a right external rectus palsy developed. Cerebellum aspirated after death and a large quantity of pus obtained.

In this case the presence of meningitis sympathica pointed to the presence of intracranial suppuration and warranted further exploration at the time of the first operation.

The following history is unique in that the meningitis sympathica was due to an abscess in a tumor adjacent to the brain:

CASE II.—E. H., admitted February 11, 1911. Illness began five days ago with peritonsillar abscess, which ruptured spontaneously thirty-six hours before admission. Patient was suddenly seized with a severe chill and vomiting. Twelve hours before admission became comatose.

Physical Examination. Patient comatose; temperature, 106° F. Marked rigidity of neck; cheeks flushed; breathing deep and stertorous. Right pupil larger than left. Shrapnell's membrane congested in left ear, otherwise ears were negative. Babinski and Kernig signs present.

February 11, 1911. Spinal fluid shows 100 per cent. polymorphonuclears and an absence of bacteria, indicating presence of a meningitis sympathica. Patient continued to have temperature up to 106.6° F. Rigidity disappeared, also Kernig's sign. Breathing labored and stertorous. Pupillary reflexes lost. Pulse became very slow and died.

Autopsy. Brain: On the left side of the sella turcica was a soft, grayish-red tumor mass about the size of a peach-stone, which had forced the optic chiasma and the corpora mammillaria to the right. Extending forward from this tumor mass, and seemingly continuous with it, was a cystic mass lying in a pit on the inferior surface of the posterior part of the left olfactory lobe. When this cyst was opened, thin yellow pus exuded. The convolutions of the brain were flattened and the surface was congested.

Diagnosis. Meningitis sympathica; infected tumor of the hypophysis; peritonsillar abscess.

Occasionally a brain abscess may be present, associated with a marked meningitis over the convexity of the hemispheres, which gives rise to a meningitis sympathica. The spinal fluid contains no demonstrable bacteria. The presence of such an extensive process cannot be diagnosed.

CASE III.—A. C., admitted November 28, 1910. For two weeks before the present illness patient had occasional abdominal pains. Five days before admission had severe abdominal pains and headache. Vomited once the day before admission. Strabismus, rigidity of neck, and flatness of one side of the face were noted the day before admission. Involuntary urination and defecation. For two days before admission had not spoken; lies quietly unless disturbed. No ear discharge.

November 29. Patient stuporous but can be aroused. Cheeks flushed; lips red; MacEwen sign present, together with marked rigidity. Eyes: Left external rectus palsy; pupils equal and regular; contracted; react to light; fundi show marked edema of both optic nerves, more on the right side; veins engorged; retina cloudy; no hemorrhages. Extremities: No palsies; reflexes active. Abdominal reflexes diminished on the right side; marked Kernig. Slight hyperesthesia of right arm and chest. Von Pirquet negative. Spinal puncture yielded 30 c.c. of cloudy fluid under tension. Spreads of cerebrospinal fluid negative for bacteria. Smears show almost entirely polymorphonuclear leukocytes; 30 c.c. of Flexner's serum introduced. Patient semiconscious; does not speak.

November 30. During the morning patient had Jacksonian epileptiform seizures limited to right side of face and arm and occasionally involving the right leg. Attacks every ten to fifteen minutes.

November 30. 9 P.M., 40 c.c. of fluid removed under a pressure of 210 mm. 11 P.M., sudden attack of cyanosis and heart failure, with death.

Autopsy. Brain: Very recent brain abscess formation in the cortex, with a perivascular infiltration of polymorphonuclear and mononuclear leukocytes in the vessels in the neighborhood of the abscess. Thick, greenish-yellow pus covered the convexity of the brain, but most marked in quantity over the left hemisphere, principally in the motor region. The pus was also present over the cerebellum, the base of the brain, and the pons and upper cord. It had collected under the pia in the interpeduncular space. The pia everywhere was markedly congested. The fluid in the lateral ventricles were moderately turbid. There was a small abscess of recent origin in the right lateral lobe of the cerebellum.

Wolf[4] reports a case in which turbid spinal fluid was sterile and

[4]Cited by Koerner: Die Ohrenheilkunde der Gegenwart und ihre Grenzgeb.

contained numerous red cells and leukocytes. The autopsy showed an uncomplicated abscess in the temporal lobe. In discussing this case, Leutert assumed that a healed miningitis was responsible for the changes in the spinal fluid, but such an hypothesis is unnecessary because meningitis sympathica occurs without any inflammatory process in the meninges.

Ruprecht[5] reports an autopsy in a case of uncomplicated abscess of the temporal lobe in which cloudy spinal fluid under increased tension was obtained before death. It contained a sediment of polymorphonuclear leukocytes and no bacteria either in smears or cultures.

Meningitis sympathica may be the forerunner of a developing meningitis purulenta and therefore its early recognition is of great importance. This is specially true in those cases in which the clinical symptoms of the meningitis are more prominent than are those of the brain abscess.

Case IV.—A child, aged two years, was kicked by a horse and received a scalp wound on the right side of the forehead. It was not unconscious and there were no symptoms of increased intracranial pressure. It had had high fever nightly for some time before admission to the hospital and had lost weight. Examination revealed a depression over the right frontal bone, rigidity of the neck and slight Kernig. Thirty c.c. of slightly turbid fluid under considerably increased pressure was obtained by lumbar puncture. The fluid showed increased albumin content and cell increase, but the mononuclear leukocytes were 99 per cent. and the polymorphonuclear leukocytes only 1 per cent. The fluid was sterile. Six days later a second puncture gave a similar result. On the succeeding day a craniotomy revealed a subdural abscess underneath the depressed bone. Seven days later, the child not improving, a third lumbar puncture yielded cloudy fluid under very high pressure. This fluid now showed an increase in the number of cells, all polymorphonuclear and streptococci in culture.

The meningitis sympathica had changed into a meningitis purulenta and the child died. Had the significance of the meningitis sympathica been recognized the operation for cerebral abscess could have been performed at once with greater possibilities of therapeutic success. The following case illustrates this point:

Case V.—Admitted to the service of the late Dr. Gruening, complaining of pain in the left ear and left hemicranium. Twenty c.c. of turbid fluid was obtained. The cells, increased in number, showed 84 per cent. polymorphonuclear and 16 per cent. mononuclear leukocytes. No bacteria present. Radical mastoid operation performed. The dura exposed and found to be pulsating, but covered with a layer of greenish-colored fibrin. Upon exploration a large epidural abscess containing foul-smelling, greenish pus was

[5] Arch. f. Ohrenheilk., l, 221.

discovered and evacuated. Four days later clear fluid was obtained under normal pressure. The patient made an uneventful recovery.

The presence of the turbid spinal fluid undoubtedly prompted the operator to explore beyond the mastoid in this case. It is furthermore important to note that the abscess was an epidural one, and yet by its irritation gave rise to the meningitis sympathica.

It occasionally happens that meningitis sympathica may be present and yet cause no symptoms. Its early recognition is always important, not only because of the prognosis but also of its bearing upon the treatment. In fact, I feel that an examination of the spinal fluid should be made in every case of mastoiditis before operation.

At times an old middle-ear infection may cause an epidural inflammation by extension. The mastoid symptoms may be absent but the meningitis sympathica indicates a suppurative focus near the meninges. The following case is one in which the surgeon was probably led to radical exploration by its presence:

Case VI.—D. B., admitted July 27, 1908. Discharge from both ears in childhood. Present illness began, with sudden severe pain in the left mastoid region. No discharge. Fever and chills.

July 27. Physical examination: Right ear: shows moderate granulations. Left ear: the upper and outer part of the middle ear filled with cholesteatomatous material. No edema. Marked tenderness over the mastoid. Eyes: veins of both fundi are dilated. Neck: rigid and head retracted. Marked Kernig sign. Pulse: 58 to 60. Lumbar puncture: 20 c.c. of turbid fluid under increased tension. Fluid contained leukocytes and no bacteria. Diagnosis lay between sinus thrombosis or a suppurative process near the meninges. Operation: Dr. Koller. Dura found pulsating and covered with greenish fibrin. Flow of blood free from sinus. No thrombosis. Sinus packed with gauze.

July 30. Temperature dropped to 100° F.

July 31. Lumbar puncture: 30 c.c. of clear fluid under normal tension.

August 5. Temperature normal. Slight rigidity of neck; slight Kernig sign. Sinus wound healthy. Upon removing drainage tube a fairly large quantity of cerebrospinal fluid discharged.

August 11. Opening closed. Headache which existed for last few days had ceased. Uneventful recovery.

This was a case in which the absence of bacteria in the blood pointed against sinus thrombosis and the sterile spinal fluid against a suppurative meningitis.

Grossman[6] reports a case which is interesting because the meningitis sympathica appeared after the mastoiditis had been cured.

[6] Arch. f. Ohrenheilk., vol. lxiv.

The autopsy revealed a thrombosis of the superior petrosal sinus and no meningitis. He considered the case one of so-called otitic sepsis.

The persistence of meningitis sympathica in a case in which there is a known suppurative intracranial focus, is almost positive indication that the focus has not been found and treated. The following case supports this assertion and furthermore demonstrates the possibility of the meningitis becoming a true infective process.

CASE VII.—M. G., admitted August 12, 1908. Four years ago had pain in right ear. Drum incised. Ear discharged pus for three months. Six weeks ago had gangrenous appendicitis. Eight days before admission had profuse discharge from right ear. Two days later had severe headache. Temperature, 102° F. Prostrated; vomited several times. Marked rigidity of neck; herpes labialis. No chill; no pain over mastoid.

Physical Examination. Mastoids; no tenderness or swelling. Knee-jerks exaggerated. No clonus; no Babinski. Neck rigid. Kernig marked. Symptoms pointed to a meningitis which did not appear to be of the ordinary cerebrospinal type. Ear regarded as the probable cause. Lumbar puncture: 25 c.c. of turbid fluid under markedly increased tension. Polymorphonuclear, 80 per cent. No bacteria found. Aseptic polymorphonuclear meningitis was diagnosed and operation for brain abscess advised.

August 13. Operation: Dr. Wolff. Right mastoid cells were found practically sclerosed. Antrum exposed and found filled with a mass of cholesteatomatous material, as was also the middle ear. Sinus normal. Dura exposed and found pulsating. No epidural abscesses. It was not considered advisable to aspirate the brain at this time.

August 14. Pulse, 72 to 80; headache; less pain over right ear. Right facial palsy. Cerebrospinal fluid; 85 per cent. polymorphonuclear leukocytes.

August 15. Patient better. Much less headache; less rigidity of neck; Kernig less marked.

August 19. Some edema of the eyelids, especially the lower. Eye-grounds: edema; infiltration of both retinæ, especially on left side. Retinal vessels are raised and structure of retina looks blurred.

August 22. Eyes examined by Dr. Friedenberg. Pupils dilated. Right disk slightly hazy; veins tortuous; retina near disk slightly edematous. Slight pallor of temporal half of disk.

September 6. First dressing. Profuse discharge from mastoid. Since operation patient has had a temperature of 99° to 102° F. Patient has rigid neck and Kernig's symptoms.

September 7. Very profuse discharge. Wound still open.

September 12. Packing removed. Rigidity of neck and Kernig not so marked.

September 20. Lumbar puncture. Cloudy fluid; polymorphonuclear, 71 per cent.

September 22. Meningitis symptoms still marked. Lumbar puncture; 25 c.c. of turbid fluid withdrawn. Polymorphonuclear, 85 per cent. After each puncture the patient's symptoms were temporarily relieved.

September 24. Symptoms still present. Patient worse. Temperature, 103° F.; pulse, 80.

Exploratory Craniotomy. Dr. Oppenheimer; to locate focus. The dura under marked tension. Area of dura about the size of a 50-cent piece exposed. No pus or purulent cerebrospinal fluid escaped. With a scalpel, punctures of the brain were made in four or five directions, but each time with a negative result. Dura closed. Line of suture closed by Cargile membrane. Wound packed with iodoform gauze.

September 26. Following the operation the symptoms were more marked. Patient delirious. Lumbar puncture. Fluid under tension and almost pure pus.

September 27. Condition relieved after lumbar puncture. Rational a short time; ceased.

Note. The first cerebrospinal fluids contained no bacteria; when the patient became very sick again the fluid contained bacteria microscopically, but they would not grow. After the operation pure pus was found; it was considered probable that a brain abscess had ruptured.

Autopsy. At the apex of the petrous portion of the temporal bone there was an area of caries and necrosis. The pus was foul, thick, and greenish. It contained a variety of bacteria, most of which were Gram-positive bacilli. No abscess could be found anywhere in the brain, but the presence of practically pure pus in the cerebrospinal canal shortly before death shows that an abscess which was probably present previously had ruptured into the ventricle. The patient evidently had three attacks of so-called "meningitis sympathica." These were probably due to an infection of the canal by anaërobic bacilli which did not multiply sufficiently to cause progressive meningitis.

Meningitis sympathica may also be present in patients in whom there is an inflammation of the accessory sinuses of the cranium or even in the structures adjacent to it.

Case VIII.—Patient suffering from orbital cellulitis of nine days' duration; admitted to the service of Dr. Elsberg November 29, 1913. Orbit incised and drained. The next day lumbar puncture; 15 c.c. of turbid spinal fluid under tension. Cells increased and all polymorphonuclear. The fluid contained a contaminating Staphylococcus albus. This finding means that there was a meningitis sympathica and that the inflammatory process or a toxin had reached the meninges.

Patient considerably improved by operation, and yet irritation of the meninges warned against a too hopeful prognosis. Thirteen days following the operation, although the patient was doing well, I requested another lumbar puncture; 20 c.c. of slightly turbid fluid under a pressure of 160 mm. obtained. It contained 133 cells to the cubic millimeter, with a greater proportion of mononuclear than polymorphonuclear leukocytes. Albumin content increased. Cultures sterile. These findings were a positive indication that the patient was not out of danger.

Patient left hospital apparently cured December 30, 1913.

March 10, 1914 (three months after discharge), readmitted because of severe headaches in the right temporal region. No evidence of accessory sinus disease. Eye examination negative. Lumbar puncture: clear fluid under increased tension, but without an increase of cells. Patient discharged with the diagnosis of periostitis of the frontal bone.

June 25 (three months after his second discharge), readmitted because of severe headaches in the same region as previously. Drowsiness and vomiting; symptoms of intracranial pressure. After admission he had a convulsion. Lumbar puncture: fluid under pressure, with increased albumin content, increase of polymorphonuclear leukocytes, and no bacteria. This was evidence of renewed meningeal irritation. Operation: frontal lobe exposed. It appeared soft and the pia over it was edematous, but no abscess was found.

August 20. Discharged, improved.

He was subsequently admitted to another hospital, where repeated lumbar puncture yielded sterile turbid spinal fluid. A diagnosis of brain abscess in the right frontal lobe was made and the lobe explored, but without result. Autopsy revealed an abscess in the lobe.

This case therefore shows how an inflammation which in the beginning is not intracranial may cause meningitis sympathica and that the latter's presence may be of great importance in determining the prognosis and the treatment.

Reischig[7] reports a case of meningitis sympathica dependent on suppuration in the anterior sphenoidal cells under the name of meningitis aseptica.

Meningitis sympathica is of clinical significance when it occurs in association with a known or suspected intracranial suppurative condition. It is very difficult, if not impossible, to differentiate it occasionally from the condition known as meningitis aseptica. In this latter disease the spinal fluid possesses the same characteristics as the fluid in cases of meningitis sympathica, except that it may be more turbid and contain a greater number of leukocytes. The

[7] Zeit. f. Ohrenheilk., 1913, Bd. 69, p. 78.

differential diagnosis between the two depends upon the presence or absence of a possible inflammatory cause. It is probable that many of the reported cases of meningitis aseptica were really cases of meningitis sympathica and that they recovered without discovery of the primary suppurative condition in the brain or adjacent structures.

One of the most recently reported cases of this class, namely, that of Zabel,[8] is not a case of meningitis aseptica, but primarily one of subarachnoid hemorrhage in which the secondary reaction of the meninges was evidenced by an accumulation of leukocytes which caused a turbid fluid. In many of the cases there is a history of trauma which may precede the development of the meningitis by as much as a year. Some of these cases apparently recover and leave the suspicion that there may be a latent abscess remaining.

There is also some question in both meningitis sympathica and meningitis aseptica whether bacteria may not at some time have been present in the spinal fluid. Occasionally meningococci cannot be found in spreads or grown in cultures from the spinal fluid; especially in old or subacute cases of meningitis. Concetti, Oseki and others believe that bacteria are destroyed by the spinal fluid for a time or else lie in the meninges. This may account for the number of cases in which Mygind[9] found an extensive meningitis at autopsy and yet could find no organism in the spinal fluid during life. He reports 24 sterile fluids out of 61 clinical cases of meningitis. In 12 of the 24 cases the presence of meningitis was confirmed by autopsy.

Widal has pointed to changes in the cells in the spinal fluid as a means of differentiation between the septic and aseptic meningitis. In the septic meningitis the leukocytes give evidence of necrobiosis. There is destruction of the nuclei, degeneration of the cell borders, with the disappearance of the granules and the appearance of the vacuoles.

In aseptic meningitis and meningitis sympathica the cells are unaltered. In long-standing cases of these two conditions there are some changes in a few cells at a time and lymphocytes very frequently replace the polymorphonuclear leukocytes.

Cerebral syphilis occasionally presents the clinical picture of a meningitis and a very turbid spinal fluid containing a large number of leukocytes. Belin and Bauer report a case in which the fluid remained turbulent for four months; Revaut, one of two months; and Widal and Lemierre two of a few days' duration. Of course in such cases the history of syphilis and the positive Wassermann reaction aid in the differential diagnosis.

The differential diagnosis between meningitis sympathica and tuberculous meningitis is most important. When there is a known

[8] Ztschr. Ohrenheilk., 1914–15, Bd. 72, p. 73.
[9] Ztschr. Nervenheilk., 1910, Bd. 40.

focus of infection the diagnosis is not difficult, but occasionally cases are met with in which there may be considerable difficulty. As a rule the cell content in the spinal fluid in tuberculous meningitis is not increased in the early stage, and if it is the mononuclear leukocytes are predominant. But there are exceptions to this. An example of the difficulty of differential diagnosis is seen in the following case:

Case IX.—A child, aged fourteen months, was admitted to Dr. Elsberg's service in stupor, with the history of having a discharging ear two weeks previously. The child had no symptoms of meningitis, but there was a spastic hemiplegia. Lumbar puncture: fluid under pressure; 200 cells per cubic millimeter; 15 per cent. mononuclear. This cell count in itself did not indicate a suppurative intracranial process. Fluid: bacteria-free; no tubercle bacilli found. Exploration of the brain, without results. The autopsy revealed a tubercular process in the interpeduncular region.

The cerebrospinal fluid of acute poliomyelitis during epidemics is under increased pressure and contains a marked increase of cellular elements during the acute febrile period. The increase generally takes place in the polymorphonuclear leukocytes, which in some instances have been observed to be as numerous as 3000 per cubic millimeter. The fluid may be very turbid and is always sterile. In the subsiding stage there is a decrease in the number of cells with the lymphocytes predominating. In addition there are present the symptoms of meningitis. The picture therefore is one of meningitis sympathica. The diagnosis, of course, depends upon the association of the meningitis with the other symptoms characteristic of the disease, except in the abortive cases, in which the findings in the spinal fluid furnish the only definite evidence of the disease.

Polioencephalitis inferior of infectious origin may cause a meningitis sympathica, as the following case shows:

Case X.—April 14, 1913, a patient was admitted to Dr. Gerster's service suffering from an ischiorectal abscess. He was discharged in thirteen days, cured. Six weeks later he was readmitted with high fever; complete right facial paralysis; right external rectus paralysis; horizontal nystagmus; and left internal rectus paresis. No rigidity of the neck. Lumbar puncture: turbid fluid under increased tension with a great increase of polymorphonuclear. Cultures and spreads were negative. A diagnosis of abscess in the right side of the posterior fossa was made and an operation performed, with a negative result. The autopsy revealed a polioencephalitis, with softening involving the right half of the medulla.

In this case there was a focus of infection, and all the clinical symptoms pointed to the presence of an abscess as the most probable cause. Unfortunately, we frequently meet with intracranial inflammatory conditions in which there is no evidence of meningeal

irritation, but when meningitis sympathica is present it aids us both in the diagnosis and the treatment of such conditions.

The picture of meningitis sympathica may be present in cases in which there has been a subarachnoid hemorrhage, and enough time has elapsed to allow for the disappearance of most of the red blood cells. The reaction of the meninges in these cases is shown almost invariably by a very marked increase in the lymphocytes, and if the fluid does not show the presence of red cells the origin of the lymphocyte content is suggested by the peculiar yellowish tint of the fluid. This color is always diagnostic of hemorrhage unless there is reason to suspect a tumor or obstructive inflammatory lesion in the neighborhood of the spinal cord.

In cases of brain tumor in which there is an extreme degree of internal hydrocephalus, rigidity of the neck and Kernig's symptoms may occasionally be present. I have seen such a case in which, in addition, the spinal fluid was turbid and contained lymphocytes in excess. The tumor was situated in the thalamus and a hemorrhage had occurred in it directly under the ependyma of the lateral ventricle. This probably caused the lymphocytosis.

From the cases cited the difficulties of differential diagnosis of certain intracranial inflammations is only too apparent, but the finding in the spinal fluid of the properties characteristic of meningitis sympathica contributes a valuable aid for diagnosis, prognosis, and treatment.

I desire to express my indebtedness to the various attending physicians of the Mt. Sinai Hospital for permission to refer to their cases, and to Dr. E. Libman for his kind assistance and valuable suggestions.

REVIEWS

PROGRESSIVE MEDICINE. A QUARTERLY DIGEST OF ADVANCES, DISCOVERIES AND IMPROVEMENTS IN THE MEDICAL AND SURGICAL SCIENCES. Edited by HOBART AMORY HARE, M.D., Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College, Philadelphia. Assisted by LEIGHTON F. APPLEMAN, M.D., Instructor in Therapeutics, Jefferson Medical College, Philadelphia. Vol. III, September, 1917. Pp. 286; 31 Illustrations. Lea & Febiger: Philadelphia and New York, 1917.

THE third volume of this well-known and widely read review of medical progress appeared in September. Dr. William Ewart opens with an article of 77 pages on diseases of the thorax, heart, lungs, and bloodvessels. His article takes up in turn the recent literature on the respiratory function, to which he devotes 11 pages, and elaborates on the experiences gained in the present war on this subject. He then discusses the physical signs and methods of pulmonary tuberculosis, respiratory affections, pulmonary and bronchial blood functions and blood poisons, and the pericardium and heart, and the articles closes with a discussion of the recent advances in our knowledge of diseases of the thorax and its viscera.

Dr. William S. Gottheil's article on dermatology and syphilis is very interesting, showing, as it does, the recent strides made in our knowledge of autoserotherapy, the use of radium, and the various vaccines.

Edward P. Davis devotes 84 pages of the volume to his specialty, obstetrics, 34 of which are taken up with a discussion of the literature on pregnancy. This is followed with the views of various writers on the use of analgesia and anesthesia in obstetric practice. He then discusses the vaccine treatment of puerperal fever and the various advances made in the management of the puerperal period, and closes his article with an interesting discussion of the literature on the newborn.

Dr. William G. Spiller contributes the last article, on diseases of the nervous system, which is one of the most interesting in the volume. On the whole this number for September compares favorably with those in past years. S. S.

MEDICAL CLINICS OF CHICAGO. January and March, 1917. Pp. 231 and 237. Figs. 19 and 40. Philadelphia and London: W. B. Saunders Company, 1917.

THESE two numbers maintain the reputation which the excellence of the former ones has made for the series. In the January number appears a very encouraging clinic on splanchnoptosis, with accompanying skiagrams by Dr. Charles Spencer Williamson. Dr. Frederick Tice presents patients illustrating pericardiomediastinitis, pulmonary abscess, rectal stricture, abdominal aneurysm, and amebic dysentery. A clinic upon acidosis is covered by Dr. Frank Wright, including a discussion of the newer methods for detecting the condition. Dr. Walter W. Hamburger, in a discussion of achylia gastrica, emphasizes the similarity of the pains in this affection to those of hyperacidity. Dr. Ralph C. Hamill contributes two very interesting chapters, one upon certain psychiatric problems, especially neurasthenia, and the other upon acute disseminated myelitis and acute syphilitic meningomyelitis. In subsequent chapters Dr. M. Milton Portis deals with rectal carcinoma, Dr. Solomon Strouse with early pulmonary tuberculosis, alluding especially to the value of the roentgen rays, Dr. Charles Louis Mix with gastric and duodenal cases, Dr. Isaac A. Abt with disease resistance in relation to the nutrition of infants and with decomposition, the final ones being devoted respectively to barium diagnosis by Dr. James T. Case and purpura hemorrhagica by Dr. Arthur F. Beifeld.

The March number also presents clinics of Drs. Tice, Abt, Williamson, Hamill, Beifeld, Strause and Mix. Dr. Herman L. Kretschmer discusses the fulguration treatment of bladder papillomata, which is more properly a surgical condition, as is also a clinic upon specific urethritis by Dr. B. C. Corbus. The relationship of oral foci of infection to systemic disease is refreshingly presented by Dr. H. H. Schuhmann, who, though a Chicagoan, is not convinced of the correctness of Rosenow's findings. Dr. Frank Smithies covers the diagnostic features of retroperitoneal sarcomata, and the number concludes with a consideration of constipation by Dr. Joseph C. Friedman. T. G. M.

PULMONARY TUBERCULOSIS: ITS DIAGNOSIS, PREVENTION, AND TREATMENT. By W. M. CROFTON, M.D., Lecturer in Special Pathology, University College, Dublin, etc. Pp. 122; 20 illustrations. Philadelphia: P. Blakiston's Son & Co., 1917.

THIS little volume on pulmonary tuberculosis deals with bacteriology, anatomy, histology, physiology, methods of infection,

pathology, diagnosis, prophylaxis, treatment, and the manufacture of vaccines. If one grants there is a need for so small a sketch of so large a subject he at least wonders why some topics like diagnosis receive rather scant attention and others, like vaccines, attract a considerable amount of consideration. The discussion of unsettled questions also occupies a relatively large space. At the same time the author has included a good deal of valuable material. Emphasis is laid on the part secondary organisms play in producing symptoms and on the value of treating these invaders with vaccines. Regarding prophylaxis against tuberculosis, the author says: "Everyone gets the infection. Since this is so it seems an almost hopeless task to try and cut off the source of infection, and we must therefore place our reliance on the individual resistance," and preventive measures other than increasing individual resistance are disregarded. The reasons for employing iodoform therapeutically are not convincing, but the author enthusiastically recommends its use. The experience of the author with therapeutic pneumothorax in suitable hemorrhage cases corroborates the results of many others. Mention is made of two cases of hemoptysis developing anaphylaxis following the injection of normal horse serum given by the intravenous route. C. M. M.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Examination of a Regiment Infected with Bacillus Paratyphosus A, with Special Reference to Normal Carriers.—The occurrence of Bacillus paratyphosus A in the stools of men exposed to infection with this organism is reported by KRUMWIEDE (*Jour. Infect. Dis.*, 1917, xxi, 141), who examined the stools of 843 men of the 14th Infantry, New York N. G., after their return from the Mexican border. This regiment had been badly infected with Bacillus paratyphosus A, about 215 cases of paratyphoid infection having been diagnosed among 1000 men. Fifty-seven cases of the disease were included in this number, and among them the percentage of positive findings in the stools was much greater during the first week of the disease than in typhoid fever, being 83 per cent. In the second week 50 per cent. of the cases showed bacilli in the stools, and in the third and fourth weeks the percentage fell, unlike typhoid, in which the percentage of positive findings increases from the first week, reaching the maximum during the third week. Excluding these 57 cases there were 786 men examined, of whom 32 or 4 per cent., gave positive fecal results. None of these men gave any history of illness previous to or succeeding the examination. These histories were in all probability reliable, so that the positive cases should be considered normal carriers, that is, men who without suffering the disease, harbor and excrete the bacilli usually for a short length of time. The percentage of carriers (4 per cent.) is very high, but probably explainable by the high degree of exposure to infection. The authors used in the examination of the stools a brilliant green agar previously reported (*Jour. Infect. Dis.*, 1916, xviii, 1), and comparative results with Endo plates were greatly in favor of the brilliant green agar, the Endo plates giving only 52 per cent. of the total positives obtained upon the dye agar.

SURGERY

UNDER THE CHARGE OF

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Treatment of Recent Gunshot Wounds with Bismuth-Iodin-Paraffin Paste.—COLLEDGE and HAMMOND (*Lancet*, July 14, 1917, p. 49) say that a large number of cases have now been reported in which the bismuth-iodin-paraffin paste (B. I. P. P.) has been employed, with satisfactory results, in cases suppurating freely. The writers wish to record their experience in recent wounds as encountered in a casualty clearing station and to advocate its use in recently infected wounds in which suppuration has not yet been established. The method rightly used has the following advantages: The wound can be closed by sutures, rendering prolonged drainage unnecessary, and in the great majority of cases there is no suppuration. No change of dressing is required and much disturbance of the patient is avoided—a most important matter to freshly wounded men to whom rest is essential. It greatly increases the facility and reduces the discomfort of transport, apart from wounds of the viscera and central nervous system, the management of compound fractures presents the most difficult problem for the surgeon in a casualty clearing station, and it is in this class of cases that the writers have found the method particularly valuable. The technic is described as follows: The patients usually arrive in a filthy condition, encrusted with mud. The skin around the wounds, for now they are usually multiple shell, bomb, or grenade wounds, is cleaned with ether soap and rendered as surgically clean as possible. The part is surrounded with dry sterile towels. Surrounding the entry and exit wounds there is always a margin of necrotic skin heavily infected with microörganisms. This is removed by excising a ring of skin one-eighth of an inch wide. The wound is then freely opened up and all foreign bodies and loose pieces of bone are so far as possible removed. Further, all devitalized muscle is resected and bleeding-points secured. This resection extends not only to muscle, which is obviously necrotic, but also to areas which are devascularized and non-contractile. It is in muscle in this condition that gas gangrene begins to spread. Although this procedure is most important, the writers have had long enough experience to know that in itself it is insufficient to prevent the subsequent development of obvious signs of infection in compound fractures. The raw surface is then well swabbed with methylated spirit, and the B. I. P. P., consisting of 2 parts of iodoform to 1 of bismuth subnitrate, with sufficient liquid paraffin to produce the consistency of Devonshire cream, is smeared all over the wound and the ends of bone with a piece of dry gauze. It should be well rubbed in to form a thin film on the surface, and care should be taken not to leave any excess. It is convenient to leave the ligaturing of bleeding-points until this stage, as otherwise the ligatures

are apt to be rubbed off. Gaps in muscle can be brought together by catgut stitches when necessary. The wound is then sewn up with interrupted fishgut sutures and a dressing of dry sterilized gauze is applied; this is covered with wool, and, if required, a splint is applied. In favorable cases the dressings need not be disturbed until the patients are evacuated to the base, as it is an invariable rule to examine the wound before the patient leaves. If the outer dressing becomes stained with discharge it should be changed without disturbing the gauze in contact with the wound. If the patient has to be evacuated immediately to the base it is advisable to insert the fishgut stitches, but to leave them untied or only loosely tied. They can then be tightened later on without fear of tension being caused in the wound by retained discharge. This applies particularly to very extensive wounds. The writers conclude: The method is applicable to recent as well as to wounds several days old. There is no increased liability to gas gangrene if care be taken to eliminate that danger by free incision of damaged tissue. It is the simplest and most reliable method the writers have had the opportunity of employing of avoiding suppuration in infected gunshot wounds. It contributes greatly to the comfort of the patients for the following reasons: wet dressings and irrigations are avoided; and as the dressings need seldom be changed there is a minimum disturbance of the injured part.

Laceration of the Inferior Cava Repaired by Suture; Recovery.—COLE (*Ann. Surg.*, 1917, lxvi, 43) says that an investigation of the literature shows very few instances of extensive lacertion of the inferior cava with recovery. While separating dense adhesions from a rapidly growing tumor in the upper right quadrant of the abdomen, two longitudinal rents were made in the anterior surface of the inferior cava, one about 3.5 cms., and the other about 1 cm. in length. A very profuse hemorrhage was controlled temporarily by a gauze pack. The first efforts to disclose the nature of the hemorrhage were unsuccessful. The pack was finally held firmly compressed by the assistant's hand, and the tumor rapidly removed as the patient was almost exsanguinated. The vena cava was finally exposed sufficiently to allow an ordinary serrated Pean type clamp to be placed upon the vena cava below the rent, a gauze sponge on a sponge holder controlling some slight oozing from above. Both lacerations were quickly whipped over with a single stitch of fine catgut on a fine needle. Upon removing the clamp and sponge there was very little oozing. The entire cavity was rather loosely packed with iodoform gauze and the retroperitoneal edges were stitched to the anterior peritoneal wall. The patient was pulseless at the end of the operation, but was carried through a quite exciting twenty-four hours with intravenous saline, and was discharged from the hospital within three weeks with the abdominal wound practically healed. Ten days after the operation the patient developed a quite extensive edema of his entire right leg. This persisted for several days but gradually disappeared by the tenth day. Two months after operation the patient had had no further complication.

THERAPEUTICS

UNDER THE CHARGE OF

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The Treatment of Pernicious Anemia.—LARRABEE (*Boston Med. and Surg. Jour.*, 1917, clxxvi, 553) says that it is still unfortunately true that we do not know the cause of pernicious anemia and that we must still regard it as invariably fatal. Much has been learned concerning its pathogenesis. The systematic treatment of pernicious anemia, in the opinion of the author, should be based upon the following plan: Every case should receive arsenic, best administered continuously by mouth. If the Wassermann reaction is positive or if there is other evidence of syphilis, salvarsan should be used. Iron should seldom be given except during recovery from relapses, where the increase in red blood cells outstrips the increase in hemoglobin and the blood picture approaches that of benign anemia. The diet should always be carefully regulated with a view of controlling protein putrefaction and intestinal indigestion and preserving the nutrition. Hydrochloric acid and other aids to gastric digestion should be used freely. When the anemia is rapidly increasing, the careful use of catharsis and regular and thorough lavage of the colon and perhaps also of the stomach is in order. If the anemia still progresses and especially in hemorrhagic and aplastic states, transfusion should be done. If one or more transfusions are not followed by remission it is justifiable to remove the spleen.

The Effect of Extensive Venesection and Transfusion on Kidney Lesions in Severe Acute Mercuric Chloride Poisoning.—BURMEISTER (*Jour. Lab. and Clin. Med.*, 1917, ii, 500) found that copious venesection followed by transfusion of normal blood inhibits both qualitatively and quantitatively the characteristic degeneration usually found in the epithelium of the ascending loop of Henle in the kidneys of dogs acutely poisoned by mercuric chloride. He believes, therefore, that in desperate and other cases of acute mercurial poisoning, venesection followed by transfusion should be practised in addition to other therapeutic measures now in use.

Calcium Sulphide as the Chemical and Clinical Antidote for Mercuric Chloride Poisoning.—WILMS (*Jour. Lab. and Clin. Med.*, 1917, ii, 445) says that in advanced cases of mercuric chloride poisoning the intravenous method of injecting calcium chloride solution, grain for grain of the bichloride of mercury taken, is the safest and most rapid. An advantage of the intravenous method lies in the assurance that the patient receives the required amount of the antidote, and that it is more direct. Calcium sulphide may also be administered by mouth when

the intravenous method is not practicable. When the discomfort or the condition of the patient warrants it, both methods may be used. The use of calcium sulphide by mouth may be continued until all symptoms of mercurialism have disappeared, since it is non-toxic. Recovery has taken place, when the antidote was administered by mouth, as late as twelve hours after taking 7.5 grains of bichloride of mercury, and thirty hours when administered intravenously. The calcium sulphide solution must be freshly prepared for intravenous use or it loses its sulphur and becomes ineffective. Calcium sulphide solution should not be used stronger than 1 grain to 1 ounce of water. The solution should be boiled and filtered through cotton. The calcium sulphide solution, if deteriorated, will produce severe convulsions, owing to the free action of the calcium on the spinal cord, hence the necessity of a fresh solution. When calcium sulphide is to be given by mouth it should be administered, in the tablet or crude drug form, 2 to 5 grains every hour, until an excessive amount is taken. The author believes that local antidotes in the stomach in the form of the whites of eggs and lavage with large quantities of water is useless; bichloride of mercury is so quickly absorbed from the stomach that very little remains in the stomach unabsorbed at the end of five minutes. The vomiting by this time is so profuse that if any free bichloride of mercury were still present in the stomach it would not remain long enough to cause further damage. Wilms believes that calcium sulphide is the quickest, simplest and surest antidote for mercurial poisoning at the present time. He cites experimental and clinical evidence to warrant this belief.

The Neutralization of Virus of Poliomyelitis by Nasal Washings.—Amoss and Taylor (*Jour Exper. Med.*, 1917, xxv, 507) in a series of 56 experiments found that washings of the nasal and pharyngeal mucosæ possess definite power to inactivate or neutralize the active virus of poliomyelitis. This power is not absolutely fixed, but is subject to fluctuation in a given person. Apparently inflammatory conditions of the upper air passages tend to remove or diminish the power of neutralization. But irregularities have been noted, even in the absence of these conditions. The neutralizing substance is water soluble and appears not to be inorganic, it appears to be more or less thermolabile, and its action does not depend on the presence of mucin as such. It is suggested that the production of healthy carriers through contamination with the virus of poliomyelitis may be determined by the presence or absence of this inactivating or neutralizing property in the secretions. Whether this effect operates to prevent actual invasion of the virus and production of infection can only be conjectured. Probably the property is merely accessory and not the essential element on which defence against infection rests.

Pertussis Vaccine—Its Value as a Curative and Prophylactic Agent in Whooping-cough.—Luttinger (*Jour. Am. Med. Assn.*, 1917, lxviii, 1461) believes that the results obtained at the whooping-cough clinic and by over 180 private physicians and health officers warrants the routine administration of pertussis vaccine for both curative and prophylactic purposes. The best time to institute the vaccine treat-

ment, except as a prophylactic, is the first and second week of the paroxysmal stage. When the proper vaccine is given and the method of the New York Health Department is employed, the disease is materially reduced in duration and severity. The presence of subconjunctival hemorrhages in prophylactic cases which were protected by the vaccine seems to point to its specific immunizing action against the paroxysms and to the fallacy of the hitherto accepted theory that these hemorrhages are due to the violence of the cough.

PEDIATRICS

UNDER THE CHARGE OF

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Observations on the Presence of Bacillus Abortus Bovinus in Certified Milk (Preliminary Notes).—FLEISCHNER and MEYER (*Am. Jour. Dis. Children.*, September, 1917, xiv, No. 3). Many workers have tried to show by experimental studies that raw milk is never a safe milk and that pasteurization is the only safe precaution. Some States have passed legislation requiring the pasteurization of all milk except certified milk. Some observers have shown that certified milk is not safe without pasteurization. The authors of this paper feel that in addition to the ordinary tests made by certifying commissions, specimens should be injected into guinea-pigs in order to observe whether or not tubercular lesions are produced. There is nothing in the literature in regard to such tests having been made with certified milk. The authors collected samples of certified milk from regular distributors and injected guinea-pigs with the specimens. Acid-fast bacilli were found in the spleens, lymph nodes, and sex organs. These were the Bacillus abortus bovinus. As a result of their work, and from a *résumé* of the literature, the authors express themselves as follows: "So far as can be concluded in a preliminary report from a limited amount of material it may be said: (1) Bacillus abortus is, for practical purposes, always present in the certified milk produced in the San Francisco Bay regions. (2) Tubercle bacilli are not present in this same milk in sufficient number to give tuberculosis to guinea-pigs, although this conclusion may prove incorrect on further experimentation. (3) If the above conclusion is correct there is no necessity for pasteurizing certified milk on account of any danger that it may possess as a disseminator of bovine tuberculosis to infants. (4) It is not unlikely that in many previous milk tests for tubercle bacilli the anatomical lesion of bovine abortion disease in the guinea-pig were mistaken for tuberculosis. (5) If the Bacillus abortus is present in certified milk to the extent evident from these experiments it is difficult to consider it pathogenic for infants without it, so far as it is known, ever having produced recognizable lesions on postmortem examination. (6) The result of this work, however, is one more definite indication that it is

of the greatest importance that the abortus problem should be considered from every angle to be absolutely certain of its bearing on the health of infants."

Aural Complications of the Exanthemata.—Lynah (*Arch. Pediat.*, August, 1917, xxxiv, No. 8). The percentage of acute suppurative otitis media in the exanthemata is governed by the degree of severity and the duration of the nasopharyngeal lesion at the onset of the disease. In diphtheria the percentage of ear infections varies from 2 to 4 per cent., the greatest number being in the intubated cases. In intubated cases fed gavage 6 to 10 per cent. developed ear complications. In scarlet fever the percentage is seldom below 10 per cent., and is sometimes as high as 30 per cent. Most aural complications occur early during the first to the third week, but they may occur as late as the tenth week after scarlet fever. The author thinks that the local nasopharyngeal lesion was wholly responsible for all of the otitic complications. In measles the percentage of aural complications varies with the severity of the infection from 10 to 12 per cent., but may be as high as 20 per cent. Most of the infections develop in the catarrhal and postcatarrhal stages, and seldom later than the second week. Sometimes the ear complications in measles are extremely violent, and the writer of this paper has seen a case in which middle ear and mastoid disease developed on the fifth day and acute purulent labyrinthitis developed on the eighth day, the patient dying two days later. "Pain was frequently masked at the onset, and as a constant sign was rather unreliable; hardness of hearing might make its appearance early and always called for prompt aural examination. The temperature was invariably high at the onset in all severe cases of scarlet fever and measles, and the otitic complications seemed to have no more influence on the temperature curve than the necrotic throat lesion or cervical glands. In many instances subperiosteal abscesses might develop with no rise in temperature, and it was not infrequent in scarlet fever and measles to find extensive destruction of the mastoid process and the temperature not be elevated over 99°. The temperature curve, while usually an important symptom, was frequently subject to wide variation." Such complications as brain abscess, sinus thrombosis and the like were rare. Surgical treatment is recommended. Free incision of the drum is preferable to spontaneous rupture. In complicated cases surgical results were not gratifying. "In all cases of exanthemata the aural condition should be carefully followed from day to day, or else aural complications might be far advanced before the condition is recognized."

Phenolsulphonephthalein Elimination in Infants and Young Children.—Gittings and Mitchell (*Am. Jour. Dis. Children*, September, 1917, xiv, No. 3). This paper is based on a study of 75 cases. Males were used in order to facilitate the collection of the urine. The ages varied from three weeks to ten years. The technic differed somewhat from the usual technic followed for adults. No preliminary catheterization was performed, but the older children voided before the test. The infants and younger children were placed on Bradford frames with a clean pad of cotton under them. If any urine was lost during the test the results were discarded. 0.5 c.c. of a solution containing 3 mgs. of

phenolsulphonephthalein (half the adult dose) was injected deeply into the lumbar muscles. Catheterization at 70 to 120 minutes or both was performed except in the older children who could void. The specimens were alkalinized and diluted to 500 c.c. instead of to 1000 c.c. to allow for the half-dose administered. As a result of these tests the following conclusions were reached: "(1) The observation is confirmed that the elimination of phenolsulphonephthalein is not markedly decreased in any disease other than renal. (2) Even the youngest infants and children show about the same capacity for phthalein elimination as do adults. (3) Preliminary catheterization in the absence of retention of urine is unnecessary. (4) For purposes of comparison a uniform technic should be adopted and maintained. (5) We believe that in children a single collection exactly two hours after the injection into the lumbar muscles of 6 mgs. of phthalein should be the method of choice. The necessity for continuous or repeated catheterization would thereby be avoided. (6) An entirely different standard must be used for the accelerated output resulting from the intravenous injections. The latter need only be employed when local conditions, such as marked edema, prevent the use of the intramuscular route."

OBSTETRICS

UNDER THE CHARGE OF

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Death during the Puerperal Period from Rupture of the Bladder.—HUXLEY (*Jour. Obst. and Gynec. Brit. Emp.*, June–August, 1915) reports the case of a primipara, whose fetus was in the right occipito-posterior position, who was delivered by her physician by forceps. The physician instructed the nurse to catheterize the patient, but this was not done, as it was thought that the bladder was emptied spontaneously; there was a tear in the perineum which was closed. Eight days after the birth of the child, after a sudden stretching movement of the right arm, the patient was seized with violent abdominal pain, collapse, and vomiting. On admission to hospital the patient was in shock; the abdomen greatly distended, but not very rigid nor very tender. There was dulness over the pubes and evidently free fluid was in the abdomen. The patient stated that no urine had been passed for about thirty days and by the catheter about 40 ounces of somewhat offensive urine was removed. On the following morning 35 ounces were taken. Ten days after confinement the patent died. At autopsy between 2 and 3 pints of turbid urine was in the abdominal cavity and there was a free peritoneal exudate. The bladder was adhesive to the anterior abdominal wall and the posterior part adhesive lightly to the anterior surface of the uterus. The wall of the bladder was very thin, as if it had been overdistended. At the summit of the bladder fundus was a tear two and a half inches in length through which urine had

escaped. This case raises the interesting question "when and why rupture of the bladder occurred." It seems most probable that the sudden stretching movement which the patient made on the ninth day of the puerperal period and which was followed by acute pain was the active cause of the bladder rupture. In accounting for this accident it is remembered that forceps was applied to the fetal head when the bladder was distended. This produced increased pressure. The fact that the bladder had been distended had produced atony and the sudden reaching movement which the patient made had caused a strong and sudden contraction to the abdominal muscles sufficient to empty the bladder. One similar case is found reported by GENTILES (*Brit. Med. Jour.*, 1883, i, No. 3). The patient was a multipara and had suffered from retention of urine. She had an abortion at three months and developed acute abdominal symptoms, resulting in death thirty hours after. At abortion rupture was present and was thought to have resulted from expulsive labor pains acting upon the distended bladder.

Ovarian Cyst Obstructing Labor.—SALISBURY (*Jour. Obst. and Gynec. Brit. Emp.*, June–August, 1915) adds to the literature of this subject three cases. In the first the patient had been in labor six days at full term, and having strong uterine contractions. The child was dead and the head fixed in the pelvic brim in the right occipitoposterior position. There was complete dilatation and a large tense cyst filled Douglas's pouch below the presenting part. When the abdomen was opened and the uterus lifted out, a dermoid of the left ovary was withdrawn and ruptured. The cyst was removed, the uterus replaced, and the fetal head pushed into the pelvic brim. The patient was placed in the lithotomy position, the occiput manually rotated to the front, and with axis-traction forceps a large, dead child was delivered. The abdominal wound was closed, the patient making a good recovery. This is thought to have been a safer method than delivery by Cesarean section. In the second case, under the care of a midwife, a mass was felt behind the vagina above which was the fetal head. Under very strong pains a living child was born and the mass disappeared. The patient vomited once but seemed fairly well. She was admitted to hospital and the abdomen opened when a tumor of the left ovary weighing $2\frac{1}{2}$ pounds was found to have ruptured. There was a quantity of blood, serum, and mucoid material in the peritoneal cavity. The cyst and fluid were removed, a tube used for drainage, and the patient recovered. The third case was sent to hospital in labor because the doctor had found two polypi in the vagina. The patient was at full time in her third pregnancy. On admission she was having pains, the child living, and presenting as a first vertex. By palpation a small cyst of the left ovary was found on the left side. In Douglas's pouch there was a very hard, angular mass continuous with a softer mass on the left side of the pelvis. The patient's labor pains subsided, although amniotic liquid escaped before the abdomen was opened. As it was impossible to reach the tumors, the uterus was first emptied by section and a living child delivered. The pelvic mass was a dermoid of the right ovary as large as a cocoanut which contained a mass of bone and three teeth. There was also a dermoid of the left ovary above the pelvic brim. Both tumors were removed, the patient making an uninterrupted recovery.

Modern Practice in the Induction of Labor for Contracted Pelvis.—GUICCIARDI, in the clinic at Venice (*Annali di Ostetricia*, 1916, Nos. 1 and 2) has employed various modern methods in dealing with contracted pelvis. As the result of his clinical experience he has greatly limited the induction of labor. Before proceeding to induce labor, he would have the pelvis examined by the roentgen rays, and would choose a time not earlier than the thirty-fifth or thirty-sixth week. He would also not induce labor in any case where the pelvis was highly contracted. Every effort should be made in inducing labor to secure the spontaneous birth of the fetus; fetal mortality increases in direct proportion, as labor must be terminated by obstetric operations. Care must also be taken that in the endeavor to stimulate labor, voluntary uterine contractions may be set up which may destroy the fetus through pressure. In the use of forceps it is very essential that complete dilatation of the cervix and lower portion of the uterus be present. Otherwise the mother will be injured and the child also subject to severe pressure. Artificial dilatation with elastic bags should be practised if necessary before the application of forceps. Where great difficulty is found in securing proper dilatation it may be necessary to abandon delivery through the vagina. Where the head does not enter the pelvis the use of forceps is contra-indicated. Complications in labor which directly threaten the fetus, such as prolapse of the cord or the development of an unfavorable presentation and position, call for an abdominal delivery. Embryotomy upon the living fetus should be declined, and especially dangerous are violent and fruitless efforts at delivery made by unskilful persons. In highly septic cases with foul and putrid discharge, embryotomy may be more dangerous than extirpation of the uterus. The classic Cesarean section remains the method of choice with the highly deformed pelvis. Its sphere of application is steadily widening. Complications in section may arise from previous infection, from imperfect or infected suture material, from paralysis of the placental site, or other abnormal conditions affecting the uterus. In a certain number of cases sterilization must accompany the performance of section. Here the question as to whether the parents have children already must be taken into account; also the facilities which will be available in caring for a premature child. While pubiotomy will occasionally give a good result, its performance is frequently accompanied by complications, and under certain conditions it does not give a satisfactory solution of the problem. In cases in which pelvic contraction is but slight, it seems as if delivery through the vagina might easily be possible; the test of labor may be awaited. Should this fail, one has the choice between the classic Cesarean section and the suprasymphyseal method. Latzko's operation frequently gives results. In the severely septic cases it may be more prudent to do embryotomy in the interests of the mother rather than risk any form of major operation. In comparing the various methods of section the possibilities of repeated section must be taken into account. In choosing a method of delivery in contracted pelvis, the interests of mother and child, the condition of the family, and the possibilities for proper care for the infant must all be taken into consideration.

GYNECOLOGY

UNDER THE CHARGE OF

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Division of Ureter in Pelvic Operations.—When a ureter has been accidentally cut in the course of a pelvic operation, the surgeon usually has a choice of several procedures in considering the best method of repairing the damage. According to GRAVES (*Boston Med. and Surg. Jour.*, 1917, clxxvi, 149) ligating the ureter has certain advantages over anastomosis and implantation. It requires very little expenditure of time, usually an important consideration, as the operations in which the ureter is cut are generally of great severity. If the end of the ureter is properly tied, there is little danger of leakage and fistula. Hydronephrosis will occur in 80 per cent. of cases but it is not great and gradually subsides as the kidney atrophies. If a dangerous hydronephrosis should occur, the kidney may be removed at a later operation. Anuria appears in about 1.6 per cent. of cases after ligation of one ureter. It is highly probable that ureteral anastomosis is more commonly followed by fistula formation and infection than is the ligature operation. Furthermore, it is evident from the literature that most of the cases of death following ligature of the ureter have been due to shock following some extremely severe operation rather than to the closure of the ureter. Graves prefers an anastomosis to an implantation, since by the former only one organ is injured, and if a fistula or pyelonephritis ensues, the kidney may be removed and the trouble cured by one operation. On the other hand, if a fistula follows implantation of the ureter into the bladder, the surgeon then has to deal with two injured organs. The operation for reimplantation or closure of a ureterovesical fistula is, in Graves's opinion, less satisfactory than a simple nephrectomy, such as might be necessitated by trouble from ligature or anastomosis. If implantation is imperative, as might be the case in the presence of injury of the other ureter, or a functional deficiency or disease of the opposite kidney, the location of choice for implantation would be, of course, in the bladder, if the proximal end of the ureter is sufficiently long. In case of emergency the ureter may be left to drain from the vagina or carried out through the skin. Implantation into the intestine is not desirable on account of the almost inevitable ascending infection of the kidney. Implantation into the appendix or of one ureter into the other or even into the Fallopian tube are operations that have been advocated from experiments on animals and on the cadaver but probably have no practical value.

Treatment of Ectopic Gestation.—Contrary to the views of many, immediate deaths as a result of hemorrhage in cases of ectopic pregnancy were rare in WERDER's experience (*West Virginia Med. Jour.*, 1917, xi, 233) in a series of over 200 cases. There is a strong tendency in most cases for the bleeding to become checked spontaneously, especially under proper treatment, but persistent watching is required on

account of the constant danger of recurring hemorrhage. Shock is often an important factor, the elimination of which should be undertaken before operation when possible, thereby reducing the operative risk. Delay of operation is therefore generally advisable in grave cases after rupture, particularly when bleeding seems to be at least under temporary control. This will enable us to overcome the attending shock and also to gain the additional advantage of an improved circulation through the refilling of the depleted bloodvessels, advantages which will greatly minimize the risks attending the operative treatment.

The treatment of that rare but interesting form of extra-uterine pregnancy in which fetal life escapes destruction at the time the tragic symptoms occur, and continues to develop until the fetus has reached a viable age, presents some interesting features. The greatest difficulty and source of danger in this condition is the placenta, since the hemorrhage encountered in the removal of the living placenta is truly frightful and frequently fatal. Nevertheless, Werder believes that the only rational treatment is the entire removal of the placenta and sac, which can be done without undue hemorrhage if the uterine and ovarian arteries are controlled before the removal is begun. When these arteries are not accessible we may resort to compression of the abdominal aorta, by which means we can temporarily, at least, control hemorrhage until the placenta is out of the way and its principal blood supply is secured.

After-results of the Interposition Operation.—Ayres (*Am. Jour. Obst.*, 1917, lxxvi, 451) has had the opportunity of examining 37 patients upon whom the interposition operation had been performed, the examination including a cystoscopic study as well as a vaginal examination in nearly every case. Of the entire series, only 16 patients were free from some undesirable symptom, although in many cases the trouble was insignificant. An analysis of the 21 cases that presented undesirable symptoms shows that cystitis was complained of in 9 cases, prolapse of the fundus in 4 cases, recurrence of the cystocele in 2 cases, incontinence in 3 cases, persistent bleeding in 2 cases and separation of the anterior vaginal wall in 1 case. Considered from an anatomical result the appearances are better, since 30 of the 37 patients could be said to have a perfect cure of cystocele, rectocele and prolapse. One very significant fact is that out of the total of 21 unfavorable cases, 11 occurred in patients operated upon for complete prolapse. Out of the 9 cases of cystitis, 5 occurred in such individuals, while all the cases that had poor anatomical results occurred in those operated upon for complete prolapse. Ayres has analyzed the results in this series and has drawn certain conclusions in regard to the indications for the interposition operation. Obviously it is an unwise procedure during the child-bearing age and likewise is contra-indicated in cases of prolapse of the third degree, but may be used to advantage in the lesser degrees of prolapse with cystocele. When fibroids are present or a condition of fibrosis is suspected, denoted by profuse, irregular bleeding, hysterectomy should be performed and the other indications met. When the operation is indicated, large uteri should be reduced in size in the course of the operation and an effort be made to keep the bladder floor level; furthermore, one should not hope to cure incontinence without strengthening the sphincter of the bladder.

OTOLOGY

UNDER THE CHARGE OF

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The Effects of High Explosives on the Ear.—WILSON (*Jour. Am. Med. Assn.*, June, 1917). The majority of the two hundred patients exhibiting nerve symptoms were examined by the author at periods varying from within twenty-four hours to one week after the injury, and of this number 50 complained of deafness in varying degree. Seventeen of the 50 cases gave evidence of injury to the internal ear as the result of the explosion. In the remainder the deafness in many instances had been merely temporary and there had been no disturbance of equilibrium in the cases of persistent impairment of hearing. This was found to be due in some to extralabyrinthine causes, the result of an old middle-ear suppuration or an occlusion of the external canal. Of the 17 cases, 6 had definite middle-ear trouble before the concussion; of the remaining 11 with no previous history of ear trouble, 6 had evidences of a recent perforation of the drum-head and 12 complained of vertigo and gave demonstrable signs of disturbance of equilibration. In regard to the character of the injury in these cases and the treatment to be employed, the author concurs in the general opinions deduced from the existing imperative opportunity for observation, and emphasizes the importance of complete rest and recumbency for a period of at least ten days after the injury and that more immediate removal to a base hospital is liable to retard recovery by the injurious effects incident to transportation.

War Injuries and Neuroses of Otological Interest. Concussion Deafness.—MARRIAGE (*Jour. of Laryngol., Rhinol. and Otol.*, London, June, 1917). These cases the author divides into two etiological classes: those the result of continued explosion of guns firing day after day, and those consequent upon the bursting of a shell fitted with high explosive in the immediate vicinity of the patient. The former belong usually in the class of results similar to those observed in foundrymen, machinists, boiler-makers and civilians engaged in corresponding occupations and there is, usually, persistent deafness in a moderate degree if the soldiers have been long exposed. The deafness due to shell explosion is generally very extreme for a short time and is sometimes accompanied by unconsciousness. In one instance the author saw a shell burst just behind a lieutenant without wounding him, but rendering him completely unconscious for an hour. When he recovered consciousness he noted marked deafness in both ears and intense headache, but no subjective noises, and no vertigo, nor was there, either at the time or later, hemorrhage or discharge from the ears. Four days later he heard the spoken voice two feet away from each ear but high tones, as represented by a loud ticking watch, of three and a half or four feet

normal distance; not at all with the tuning-fork; both air and bone conduction were much subnormal, the former, however, being better than the latter; both drum-heads were practically normal; eighteen days after the explosion the hearing had become normal. The treatment adopted by the author in these cases is rest in bed, bromides in the early stages and later strychnin. In the matter of prognosis, time is the best consultant; if marked improvement has not been made within six to eight weeks the prognosis is bad, and even when the hearing returns subjective noises often persist. In default of an opportunity for postmortem examination in any of his cases the author infers that the seat of the concussion injury is chiefly peripheral as in the cases under his observation. The deafness was rarely associated with rupture of the drum-head, which is in accordance with the generally accepted view that rupture of the drum-head lessens the concussion effect in the middle ear; in very severe concussions the author suggests the possibility of concomitant central injury, such as hemorrhages into the pons, medulla or cerebellum. Psychical deafness as the result of shell shock is usually binaural and occurs usually in cases in which the shock has been especially severe as, for instance, being buried by a shell without visible evidence of injury. The deafness is usually absolute, there being no hearing either by air or bone conduction and it is usually accompanied by other nervous signs and symptoms, loss of voice, narrowing of the field of vision, tremors, irregular paralyses and areas of anesthesia; spontaneous nystagmus is absent. The author agrees with Milligan and Westmacott that in these cases there is a temporary suspension of neuron impulses from the higher cortical cells of the central nervous system to the periphery, their view being that the hiatus or synapse interfering with the flow of nervous stimuli is a central and not a peripheral one, for the reason that in so many of the cases of sudden blindness and sudden deafness no trace of any organic lesion, peripherally, was to be found and, moreover, the rapid recovery of a large proportion of the patients was a strong argument in favor of the supposition that none had occurred. Mr. A. Cheatte is quoted by the author as reporting 2 confirmatory cases, 1 that of a private who, during a bombardment suddenly became unconscious without any definite assignable cause and so remained for two days and on recovering consciousness was found to be completely binaurally deaf, without vertigo, and without objective evidence of an aural lesion, but for the period mentioned he could not hear the loudest shouting or even his own voice. The vestibular reaction to cold was normal. The second case was that of a Belgian soldier blown from his bicycle in the retreat from Antwerp and completely deaf in both ears, aphoric and paralyzed in his left arm and leg from that time up to July, 1916; in this case rapid recovery ensued upon electrical applications, previous forms of treatment, including hypnosis having failed. The difficulty of distinguishing this form of deafness from malingering is often great but can generally be accomplished by a thorough examination of the malingerer, who is usually sullen and defiant and fully conscious, being at some time during the tests revealed in his true character while the patient with psychical deafness has the signs and symptoms of a nervous breakdown. Among the experiences of other observers the author reports some of especial interest. Two, for instance, which under different

causative conditions exhibited similar results. One seen by Mr. S. Hastings was wounded on the right cheek by a bomb; when examined eighteen days later the manubrial vessels were injected and the tympanic cavity evidently filled with blood, the Politzer acoumeter was heard at a distance of two inches, the Rinné test was negative and the bone conduction normal. Six days later bubbles were seen in the hemorrhagic contents of the tympanum and the hearing materially improved, while at the end of a fortnight later the fluid in the tympanum had disappeared, the drum-head was somewhat retracted and the hearing for the acoumeter was three feet. Mr. A. Cheatte also reports a case of hemorrhage into the middle ear due to a parachute descent, the airman, twenty-one years of age, having descended thirteen thousand feet in four minutes. The only ill effects of this rapid change of air-pressure were impairment of hearing, a feeling of fulness in the left ear and a sensation of crackling on yawning. The left middle ear was found to be filled with blood with an intact drum-head, the hearing was but slightly decreased. Nothing was done in the way of treatment and at the end of a month the blood had disappeared and the hearing became normal.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

The Cultivation and Immunological Reactions of the Globoid Bodies in Poliomyelitis.—Amoss (*Jour. Exper. Med.*, 1917, xxv, 545). The globoid bodies of Flexner and Noguchi have a definite relation to epidemic poliomyelitis. They have been found repeatedly in lesions in both man and monkey; they have not been seen in lesions or conditions other than poliomyelitis; they have produced experimental poliomyelitis in monkeys and have been recovered from lesions so produced. Like the Treponema pallidum, they are so parasitized that they are refractory to artificial cultivation. Subcultures, however, when once established grow with comparative ease, always remaining anërobic, but becoming saprophytic and non-pathogenic. The author reports two additional cultures of globoid bodies, obtained from the nervous tissues of monkeys in which experimental poliomyelitis was produced. A bit of fresh rabbit kidney is indispensable to the original cultivations. After the virus has become less parasitic it will grow, though less luxuriantly, in media containing boiled kidney and still less abundantly

in media without any fragment of the organ at all. No cultures multiply in broth even in the presence of the kidney fragment. Adapted cultures grow freely in monkey serum with kidney, less in horse and rabbit serum and least in human serum. Amoss injected rabbits and monkeys with globoid bodies in order to develop antisera which might show agglutination and complement-deviation, and tested the sera of human beings and monkeys which had recovered from poliomyelitis against cultures of globoid bodies. The rabbits responded slightly with the production of antibodies to the injection of cultures of globoid bodies; the monkeys under the same conditions responded only when the cultures were injected into the central nervous system. The response never led to more than slight reactions of agglutination and complement-deviation with the cultures. Monkey serum showed even less agglutination and no complement-deviation. Human serum gave no complement-deviation with antigen derived from globoid bodies. The maximum agglutinative and morphological changes produced in the globoid bodies cultivated in immune monkey serum were obtained in the first generation; after several subcultures in the immune serum, the reversion to normal took place in one generation in a non-immune serum.

Arthritis Deformans as an Infectious Disease.—There is still much controversy and lack of agreement in the clinical and pathological interpretation of the lesions in chronic articular diseases. Clinically, we have a number of classifications based upon the condition of the joints as found in life. The classifications take into account mainly the outstanding features which present themselves late in the disease. Thus, the terms hypertrophic and atrophic, as applied to the joint lesions indicate such distinctive types that they are very acceptable to the clinician. The nomenclature of joint diseases has become so deeply rooted that the impression is conveyed that each term used suggests a specific etiology. Because of the chronic course of these affections it has been impossible to study the cases and the individual lesions through the entire course of the disease. NATHAN (*Jour. Med. Res.*, 1917, xxxvi, 187) has undertaken a study of the pathological lesions in joints along with an experimental investigation of infectious inflammatory processes in the joints of animals. On a previous occasion he had accepted the common interpretation that the joint conditions were either of inflammatory origin or resulted from degeneration. Following upon his present study, he is more inclined to consider a similar mode of development in both. He has found that infectious agents are the most important factors in this disease, but he, furthermore, finds that the microörganisms present in different cases are not necessarily always the same. He has, furthermore, noted that both proliferative and degenerative phenomena occur in the joints of the same individual in polyarthritis as well as in cases of monarticular disease. He points out that the localization of the infection and the regions of greatest inflammatory reaction differ in the different cases. At times it is in the epiphysis, in the subperiosteum, in the capsule or in the surrounding loose tissues. Obviously, the localization of the infectious agent will lead to a different deformity. Pathological processes occurring beneath the joint cartilages may eventually lead to its atrophy or destruction.

By means of inoculation experiments, using the streptococcus, pneumococcus and staphylococcus, he repeated the work of Lexor. He was then able to produce arthritis in various grades of intensity. In his experimental work the acute non-suppurative lesions were readily obtained, but the animals were not permitted to survive sufficiently long periods of time to attain the chronic proliferative stages or the atrophic changes observed in man. He believes that it is not the specificity of the microörganism but its virulence, the resistance of the host and its location, which determine the variations of the morbid process. In man the local clinical phenomenon of the articular disease corresponds to the experimental arthritis in animals, including the decalcification and rarefication of bone caused by the vascularization of the periosteum and marrow. He believes that it is fairly certain that the various forms of polyarthritis are caused by infection, and that, therefore, the classification of the so-called arthritis deformans into the infectious and metabolic types is no longer necessary so far as the joint diseases are concerned.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

JOHN F. ANDERSON, M.D.,

FORMERLY DIRECTOR OF THE HYGIENIC LABORATORY, PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Epidemiology of Pellagra in Nashville, Tennessee.—JOBLING and PETERSEN (*Jour. Infect. Dis.*, August, 1917) in a previous report (Ibid., 1916, xviii, 501) noted the epidemiology of pellagra based on a partial survey of the city of Nashville. In this report the physical aspects of the city, the relation of pellagra to the method of sewage disposal, the diet, as well as the evidence of the occurrence of contact in the development of new cases were fully entered into. The present paper concludes the field work connected with this survey which was amplified and completed during the summer of 1916. The authors conclude that so far as the epidemiology of pellagra is concerned, as studied under the conditions existing in Nashville, they cannot ignore the fact that the disease presents all the evidences of being in some way conveyed from one patient to another. It is practically a disease of the unsewered city areas, a family disease or almost as frequently a disease "of the house next door," and not only a family disease in the sense that the members live in the same house and eat the same food, but most frequently they found that relatives, not living under the same conditions, but frequently associating, have one after the other succumbed to the disease. The fact, too, that cases develop in houses adjoining pellagrins, previously emphasized in the report of the

Thompson-McFadden Commission, is of great importance, because the chances for the wider contact, "same block," to prevail are naturally much greater than for the lesser number dwelling in adjacent houses. The mode of occurrence of pellagra among the segregated negro colonies of the city is also of interest in this connection. To all intents and purposes the various groups live under identical economical conditions, and any variations in diet would be negligible. Pellagra occurs frequently in all except one of the groups. The only explanation possible is that there is little pellagrous contact for this group. The other negroes live surrounded on all sides by pellagrous whites; this particular group is, however, cut off from the adjacent white pellagrous population by a wide railroad trackage and on the other side is adjacent to a well-sewered non-pellagrous white zone.

Gas Production in Raw and Pasteurized Milk. — ALLEN (*Jour. Infect. Dis.*, August, 1917) states that pasteurization causes milk to become more favorable to the attack of the gas-forming colon bacillus and Bacillus aërogenes. These results seem to reinforce the impression long held by many milkmen that pure raw milk has a power of resisting changes which the same milk does not possess when pasteurized. Between raw and pasteurized milk there may be important differences, although chemical analyses may show no appreciable differences. In view of the fact that milk has its value strictly because of its relation to growth, in studying raw and heated milk, due consideration should be given to delicate biological tests which utilize growth as the means of producing comparative data. It should be more generally recognized that pasteurized milk, instead of receiving less care than raw milk, should receive greater care because of its lessened resistance to many detrimental changes which the appearance of the milk does not indicate. This is especially significant in that, in general, pasteurization has lengthened the period between production and consumption.

Studies of Bacillus Welchii, with Special Reference to Gas Gangrene. —SIMONDS (*Jour. Exper. Med.*, June 1, 1917, p. 819) states that gas gangrene develops much more frequently in wounds received on the battlefield than in those incident to accidents in civil life. This is probably due to differences in the character of the wounds in the two conditions rather than to differences in opportunity for infection with the group of organisms responsible for the disease. An examination of the uniforms of Belgian soldiers for spores of anaërobic bacteria of the group capable of causing gas gangrene showed that 90 per cent. of the uniforms of men from the trenches carried spores of organisms belonging to the group of B. welchii; and that the new uniforms as received by the Belgian soldiers, and the cloth from which these garments were made, contained spores of this group of organisms in the meshes of the goods in all samples examined. Material consisting of fragments of shells, bits of clothing and other débris, and pieces of lacerated tissues and blood clot removed from recent wounds (*i. e.*, two to eight hours old) of 20 soldiers was examined for the presence of organisms capable of causing gas gangrene. Of these, 15 contained either spores or vegetative forms of bacilli having the morphological and

biological characteristics of the group of B. welchii. Only 3 of these patients, *i. e.*, 20 per cent. of the positive cases, developed gas gangrene. In each instance the wound involved the large muscle masses of the thigh with much laceration of the tissues. The organisms reached the wounds in the form of spores only. It was only in the deep-lying injured muscle that conditions were favorable for germination of these spores and rapid multiplication of the bacilli, namely, anaërobiosis and a culture medium rich in fermentable carbohydrate (glycogen). In the pathogenesis of this infection in contaminated wounds, therefore, the lacerated muscle is the most important factor, and it is to this that attention should be directed in the prevention of the disease. After active growth in the dead muscle tissue has begun, it is probably the pressure of the gas developed from the glycogen that is responsible for the rapid dissemination of the organisms into adjacent healthy tissue. Because the presence of a fermentable carbohydrate is essential to the vigorous growth of B. welchii, and because cane-sugar has been used in the treatment of war wounds, 75 per cent. of which were found to be contaminated with spores of this group of organisms, it seemed desirable to study the effects of different concentrations of saccharose upon their growth. All of the ten strains studied multiplied rapidly and produced an abundance of gas in broth containing 5, 10, 20 and 40 per cent., respectively, of saccharose. In the 40 per cent. solutions the formation of gas was somewhat slower than in the lower concentrations. Only one strain produced gas, slowly, in 50 per cent. saccharose broth. None of the strains grew or produced gas in bouillon with 60 per cent. of cane-sugar. In the treatment of gas gangrene in the war zone, one of the most effective methods is the injection of pure oxygen gas into the affected and adjacent tissues. In order to investigate the mechanism by which pure oxygen in the tissues produced its apparent salutary effects, the gas was allowed to bubble for varying periods of time through tubes of anaërobic milk containing B. welchii. It was found (1) that different strains did not show the same resistance to the presence of oxygen; (2) that, after three hours' incubation, bubbling oxygen gas for twenty minutes through milk cultures did not appear to inhibit the growth in any way, for the tubes showed typical stormy fermentation after a further twenty-four hours in the incubator; (3) that bubbling oxygen for twenty minutes through less heavily inoculated tubes of milk caused death of the organisms in from four to twelve hours; (4) that bubbling the gas through such milk tubes for five to ten minutes did not destroy the bacteria, but either inhibited their growth or changed their ability to act upon lactose, so that there was only coagulation with little or no gas formation.

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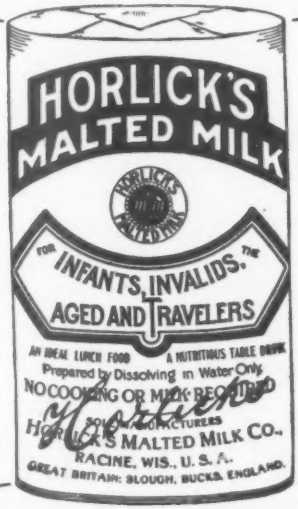
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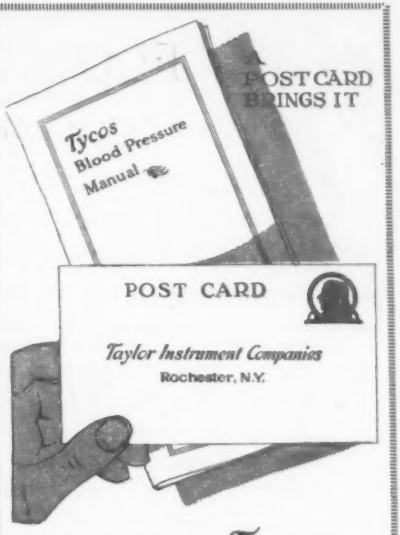

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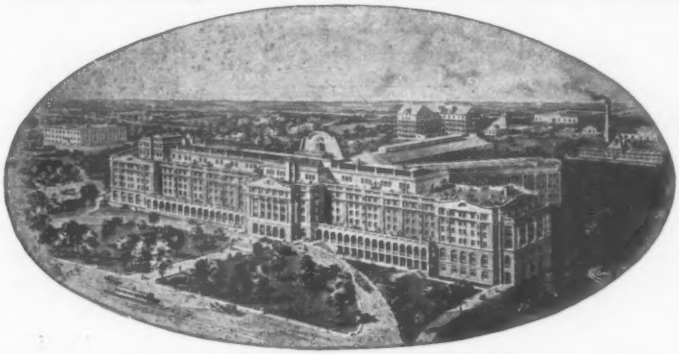

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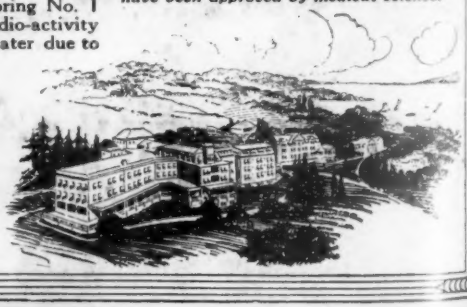

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